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RENAL CHANGES IN GOUT*

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BOSTON

THE association of renal dysfunction with gout has been stressed from the earliest writings on this disease. Garrod,[1] in 1863, stated that, "Even in slighter forms and early stages of gout, the renal organs become seriously impaired." He remarked on the frequency of albuminuria, especially in chronic stages of the disease. More recent studies by Schnitker and Richter,[2] Coombs,[3] Kinell and Haden[4] and Hench[5] give an incidence of renal impairment in gout ranging from 22 to 82 per cent. An almost equal number of patients have albuminuria without functional change. Urate gravel or stones were passed by 11 to 23 per cent of patients. Hypertension and its cardiovascular complications occur in a significant number of cases of gout but more especially in those with renal impairment.[2, 6] Hench[7] states that, as far as the life of the patient is concerned, the renal lesions surpass those of the joints in importance. Of the 17 patients with gout and nephritis studied by Schnitker and Richter 5 died in uremia.

In an attempt to clarify the pathological changes in the kidneys of patients with gout we have studied in detail the autopsy findings in 5 proved cases and 1 unproved case. Kidney tissues were fixed in Zenker's fluid, formalin and alcohol and stained with phloxine and methylene blue, hematoxylin and phloxine, Lee–Brown collagen stain, phosphotungstic acid hematoxylin for fibrils, oil red O for fat, and the silver nitrate method of DeGalantha[8] for urates.

CASE REPORTS

CASE 1. P. M. (A-49-182), a 69-year-old man, first entered the Boston City Hospital 3 months before death with complaints of weakness, nausea and vomiting. For 5 years he had experienced recurrent episodes of acute arthritis involving the knees, ankles, hands and right shoulder. For the 2 years before entry the attacks had become progressively more frequent, lasting up to 7 days, and there was residual pain and stiffness of the joints between attacks. There was a history of hypertension for 5 years, and entry was precipitated by weight loss of 25 pounds and symptoms of digitalis intoxication.

On entry the blood pressure was 180/90. There were tophi on both ears but no deformities of the joints. The urine showed negative to +++ tests for albumin and had a specific gravity of 1.013. One urine sediment contained 15 to 18 white blood cells per high-power field, and others only 1 to 3. The hemoglobin was 7.5 gm. per 100 cc. on entry, dropping to 6.0 gm. at discharge; the white-cell count was 8500, and the red-cell count 2,200,000. A blood culture was negative. The nonprotein nitrogen was 71 mg. per 100 cc.

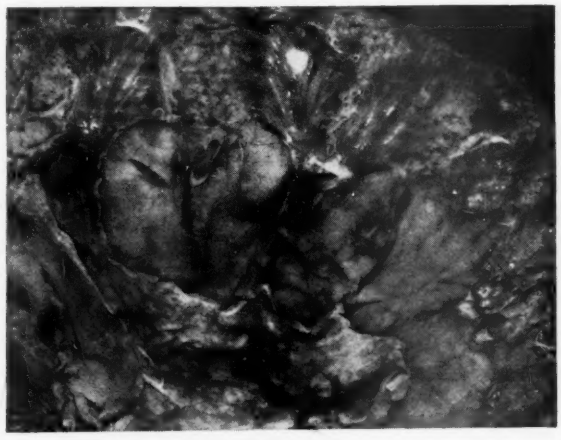

FIGURE 1. *Urate Deposits in Kidneys in Case 1.*

on entry, rose to 162 mg. but dropped to 75 mg. at discharge. The creatinine was 3.8 mg. and the uric acid 13.6 mg. per 100 cc. when the nonprotein nitrogen was 153 mg. X-ray films of the hands, feet and knees showed moderate hypertrophic changes and osteoporosis.

On the 4th hospital day there was an episode of acute arthritis in both knees that subsided spontaneously. On the 43rd hospital day the patient was able to leave the hospital.

He re-entered the hospital 3 days before death, in uremia, with a nonprotein nitrogen of 358 mg. per 100 cc. The urine had a specific gravity of only 1.010 and gave a ++++ test for albumin. The white-cell count was 20,000, with 82 per cent neutrophils. The coma deepened, pulmonary edema developed, and the patient died.

At post-mortem examination, 12 hours after death, the right kidney weighed 180, and the left 140 gm. The surfaces of both kidneys were nodular throughout and pale tan. The cortex and medulla of the left kidney contained numerous small abscesses filled with creamy pus, and there were occasional abscesses in the right kidney. The cortexes were

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narrowed to 0.2 to 0.3 cm. and were very irregular. The cut section was generally pale, with red patches at the junction of cortex and medulla.

There were numerous thin, chalk-like streaks radiating through the medullary areas toward a peak at the tip of the papillae (Fig. 1). They were generally distributed throughout

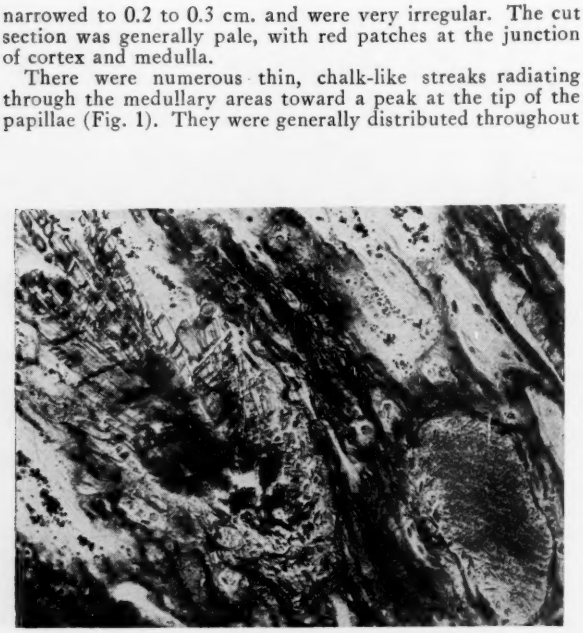

FIGURE 2. *Photomicrograph of Kidney in Case 1, Showing Small Crystals (Schultz-Schmidt Stain x250).*

both kidneys but were more marked in some papillae. There was pus in the left pelvis and ureter.

There were chalk-like deposits on all surfaces of the knee joints.

Cultures of the left kidney and heart's blood grew out *Aerobacter aerogenes*.

On microscopical examination of the kidneys the essential findings were deposits of urates in the medulla, marked chronic pyelonephritis and moderate benign nephrosclerosis. There

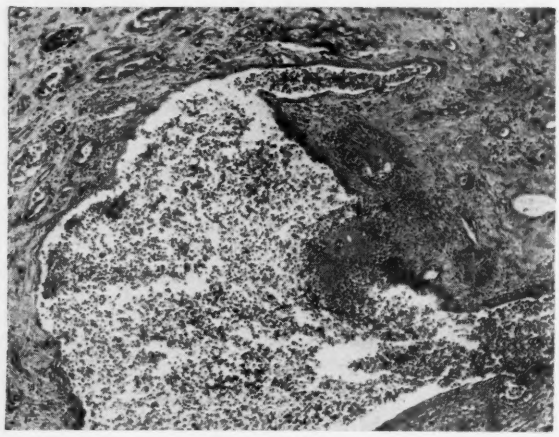

FIGURE 3. *Photomicrograph of Kidney in Case 1, Showing Urate Deposits (Phloxine and Methylene-Blue Stain x75).*

were about 15 oval or elongated deposits of urates in each section at various levels of the medulla. They conformed to the shape and direction of tubules, but no tubular epithelium was found. Some of the deposits appeared as large rhomboid, cylindrical, or needle-like crystals with several foreign-body giant cells at the periphery and mild fibroblastic reaction. There were transitions to masses of very small almost granular needle-like or rod-like crystals, often with a peripheral layer of radiating rays (Fig. 2). Spindle cells, probably fibroblasts, interdigitated with these rays and also formed an irregular fibrous capsule around the deposit, together with occasional giant cells. The surrounding interstitial tissue was increased in amount over a large area.

There were occasional thin-walled abscesses in the medulla, chiefly of the left kidney, and many of these were intimately related to or surrounded urate deposits (Fig. 3).

Most of the glomeruli were involved in dense scarring with surrounding chronic inflammatory changes and many dilated tubules filled with colloid casts. The arterioles and small arteries showed moderate hyaline degeneration and thickening. Many of the epithelial cells of the remaining uninvolved but dilated tubules contained clear vacuoles that did not stain for fat.

Death was due to renal failure as a result of severe widespread pyelonephritis. There was a terminal complicating bronchopneumonia.

CASE 2. L. S. (A-43-320), a 75-year-old man, collapsed suddenly on the day of entry. He had been treated for several years with colchicine for gout. On entry he was semistuporous and had a left hemiplegia. There was a tophus on the left ear and 1.5-cm. bunion-like masses over the proximal metatarsophalangeal joints.

The urine had a specific gravity of 1.020 and gave+++ to ++++ tests for albumin, but the sediment was normal. The blood was not remarkable, and the spinal fluid was grossly bloody. The patient never recovered consciousness and died quietly after 1 week.

At post-mortem examination, performed 6 hours after death, the combined weight of the kidneys was 300 gm. The capsules stripped with slightly increased difficulty, to reveal a rough, granular surface. There were numerous cysts on the surface of both kidneys, and there was a large cyst, 2 cm. in diameter, at the lower pole of the left. The pelves and ureters were normal, and the renal vessels were not remarkable.

The bunion-like masses over the great toes consisted of deposits of soft, white, calcareous-like material in the tissues. Similar deposits were found on the joint surfaces.

The essential microscopical findings were deposits of urates in the medulla and marked benign nephrosclerosis. The deposits of urates were of both the larger crystalline and smaller granular varieties. A few epithelial cells of tubular origin were present at one edge of a deposit of large, radiating needles, with foreign-body giant cells at another surface. The arterioles and small arteries showed marked hyaline thickening and narrowing, with moderate axial thickening of all glomeruli. Some glomeruli were in the process of vascular obliteration, and the cortex was retracted by numerous small scars. Occasional groups of tubules were dilated, and there was vacuolization and fragmentation of some of the epithelial cells.

The cause of death was a large cerebral hemorrhage on the right.

CASE 3. C. G. (A-28-78), a 70-year-old man, was admitted to the hospital 1 month before death with complaints of pains in the joints and swelling of the right knee. Physical examination revealed subcutaneous tophi over the cartilages of the ears and about the joints of the hands, wrists, elbows, shoulders, knees, and toes. These joints were stiff and moved with much crepitation. There was arteriosclerotic gangrene of the right second and third toes.

The right leg was amputated, but death followed from wound sepsis.

At post-mortem examination, performed 4 hours after death, the kidneys, whose combined weight was 410 gm., were similar in appearance. There were many firm, irregular, red, shriveled depressions on the surfaces, standing out in sharp contrast to the remaining grayish-red, pale elevated portion. The cortex was irregular in thickness, varying from 0.3 to 0.7 cm., and grayish red with moderate congestion. The pyramids were pale, and toward the apexes of a few of them, minute radiating chalk-white lines could be traced down to the papillae. The calyxes, pelves and ureters were normal.

There were urate deposits in and around many of the vertebral-column articular facets and in the epidural space, slightly invaginating the dura. Urates were also present in the joint surfaces, capsules, bursas and tendons of the sternoclavicular joints, fingers, wrists, elbows, shoulders, knees, great toes and ankles.

The amputation stump was necrotic, and tracts of pus extended upward beneath the muscles. Culture of the area grew out hemolytic streptococci and *Escherichia coli* (*Bacillus coli communis*).

On microscopical examination of the kidneys the essential changes were deposits of urates in the medulla (Fig. 4), moderate benign nephrosclerosis and occasional small bands of healed pyelonephritis.

There were a few urate deposits in each section, mostly of the larger crystalline type. These were frequently located at the apex of a band of healed pyelonephritis that showed

FIGURE 4. *Photomicrograph of Kidney in Case 3, Showing Urate Deposits in the Medulla (Phloxine and Methylene-Blue Stain x9).*

interstitial fibrosis, mononuclear-cell infiltration and many colloid casts. The arterioles and small arteries demonstrated marked hyaline degeneration, with axial thickening of the glomeruli. Many of these vessels were occluded, leaving small scars in the cortex. The tubules were generally dilated, and occasional groups of tubules had vacuolated epithelium.

Death was due primarily to sepsis of the amputation stump and bronchopneumonia.

CASE 4. F. W. (A-49-419), a 75-year-old man with bronchial asthma and moderate hypertension, had been hospitalized as an ambulatory chronic patient for about 2½ years. One year before death he had his first attack of acute arthritis of the first tarsophalangeal joint bilaterally. No tophi were present, but the blood uric acid was 7.3 mg. per 100 cc. The joints cleared completely in 1 week under colchicine therapy. He had a similar episode 4 months later. There were no more attacks before death.

The urine had a maximum specific gravity of 1.025 and gave + to +++ tests for albumin, and the sediment occasionally contained 5 or 6 white blood cells per high-power field. The blood count was not remarkable, and the nonprotein nitrogen was 42 mg. per 100 cc.

At autopsy, performed 6 hours after death, the combined weight of the kidneys was 260 gm. The capsules stripped with ease, exposing dark-red, finely granular surfaces. On section the medulla and cortex were congested. The corticomedullary demarcation was poor, and the cortex was thinned to about 0.2 cm. In many of the pyramids there were linear, white, gritty streaks, some appearing as very fine, white granules. The pelves, ureters and renal vessels were not remarkable.

There were small chalky-white deposits on the articular surfaces of the metatarsophalangeal joints of the big toes.

Microscopical examination of the kidneys revealed deposits of urates at various levels of the medulla, marked benign nephrosclerosis and a few focal areas of colloid casts, possibly representing small areas of healed pyelonephritis. There were 8 to 10 urate deposits in each section of both the needle-like radiating and the granular types. The arterioles and the medium and small arteries showed severe hyaline degeneration and thickening, many being completely occluded. All glomeruli disclosed marked axial thickening, and some showed stages of vascular obliteration and fibrosis. The tubules were generally intact.

Death was due to an acute myocardial infarction.

CASE 5.* W. R., a 68-year-old man, was admitted to the hospital in coma, with signs and symptoms of uremia. He had been ill for only 10 days with "grippe" and had been anuric for several days. There was a history of gout for many years. Tophi were present on the joints of both hands and the left great toe. The urine had a specific gravity of 1.014 and gave a ++ test for albumin. The blood urea nitrogen was 100 mg., the creatinine 11.6 mg., and the uric acid 11.7 mg. per 100 cc. The patient remained in coma and died 3 days after entry.

On post-mortem examination the kidneys were of average size, with granular cortical surfaces. The corticomedullary demarcation was well preserved, and the cortex was of average width. There were occasional small urate deposits in the medulla.

Sections of the left great toe and joints of the fingers revealed extensive deposits of urates.

Microscopical examination of the kidneys demonstrated deposits of urates in the medulla, slight benign nephrosclerosis, and lower-nephron nephrosis. The medulla contained occasional urate deposits of the large, needle-like variety. The arterioles and small arteries showed mild hyaline thickening and narrowing. There was severe degeneration of the lower tubules, blood and pigment casts and interstitial inflammation typical of lower-nephron nephrosis.

Death was due to uremia caused by the lower-nephron nephrosis.

CASE 6. J. M. (A-49-283), an 83-year-old man, had passed some urinary calculi 12 years before entry and had been catheterized for urinary retention 2 months before entry. He had been troubled with constant foot aches for many years, but the history did not suggest gout. He entered the hospital in cardiac failure, slowly became drowsy and unresponsive, and died 22 days after entry. No tophi were found.

The urine had a specific gravity of 1.018 and gave a + test for albumin, and the sediment contained 2 to 4 white blood cells per high-power field. The blood count was not remarkable, and the nonprotein nitrogen varied from 65 to 90 mg. per 100 cc.

At post-mortem examination, performed 16 hours after death, the combined weight of the kidneys was 175 mg. The surfaces were markedly granular and red. The cortex was narrowed, and demarcation of the cortex from the medulla was poor. The pyramids were streaked with small, white crystals (analysis revealed urates). Near the tip of many of the pyramids in the renal tissue were round, smooth, white stones up to 0.2 cm. in diameter. The pelves and ureters were normal.

The joint surfaces of the knees and first and second metatarsophalangeal joints were smooth and intact, and no urate deposits were found.

Microscopical examination of the kidneys showed deposits of urates in the medulla, marked pyelonephritis and moderate benign nephrosclerosis.

There were about 10 urate deposits in each section. Many of these were typical, radiating, needle-like rhomboid or granular deposits. In addition, there were long, dilated, tubule-like deposits of tiny crystals, with only a mild fibroblastic reaction, and also large masses of large rhomboid crystals, with extensive inflammatory reaction. About 50 per cent of the parenchyma was distorted by fibrosis, mononuclear-cell infiltration and colloid casts. Occasional tubules were filled with neutrophils.

*We are indebted to Dr. A. Angrist, pathologist, and Dr. W. Scharfman, intern in pathology, Queens General Hospital, New York City, for permission to include this case.

The arterioles and small arteries showed moderate hyaline degeneration.

Death was due to arteriosclerotic heart disease, with cardiac failure.

Discussion

Every kidney in this series of 6 cases had deposits of urates in the medulla. That the kidneys of most patients with gout contain such deposits is substantiated by numerous sources. All Garrod's[1] patients with chronic gout and tophi had urate deposits in the kidneys, and 6 out of 9 patients in early cases also had them; he believed that the deposits were interstitial and not in the tubules. Hench[5] reports that 2 out of 3 cases of gout showed urate deposits in the kidney tubules at autopsy, and in Talbott's[9] 9 autopsied cases the deposits were present in the tubules and interstitial tissue. Minkowski[10] described the typical gout kidney with deposits of crystalline urates, probably within dilated tubules. He believed that the first deposition occurred in the epithelium of the convoluted tubules. The epithelium desquamated; the urate deposits enlarged and were flushed down to the collecting tubules, where an inflammatory reaction occurred, destroying the tubular structure. Ebstein[11] stated that the only lesion specific for gout was a necrotic focus, with crystalline urates and reactive inflammation, and that crystals of urates alone could occur in other conditions.

In the cases reported above, the deposits conformed to the shape, direction and position of collecting tubules. Although definite tubular epithelium around the deposits could be identified only rarely, we believe that the deposits were probably originally located in the tubules. In most cases the inflammatory and foreign-body reaction to the urates had destroyed the tubular structure. The deposits may be caused by precipitation from a supersaturated solution of urates produced by the removal of water by the tubules. The work of Folin and his co-workers[12] showed that in animals the kidneys are the only organ where urates are stored and that marked excesses of urates in the blood cause a temporary renal insufficiency. This lends weight to the explanation for the production of the deposits given by Minkowski.[10]

Although each of the urate deposits was surrounded by a wide area of interstitial fibrosis it is probably unusual for this alone to produce significant renal impairment. Bell[13] reports 2 cases in which tophi in the pyramids were regarded as the cause of renal insufficiency. Case 6, presented above, may approach this, but the superimposed pyelonephritis makes evaluation difficult. A further effect of the urate deposits may be the formation of stones around them as a nidus should they be passed into the kidney pelvis. This may be a factor in the frequency of kidney stones in gout.

Case 6 showed lesions presumably specific for gout, but no definite history of acute arthritis was obtained from the wife or private physician of the patient. The blood uric acid was not measured, and no tophi or joint lesions were found at autopsy. Ebstein[11] described similar findings of contracted kidneys and typical gouty deposits, with minimal or no joint changes. He called it "primary renal gout." Umber[14] also believed that this may occur and described 2 cases of typical gout kidneys with no clinical history or other pathological findings of gout. No blood uric acid levels were mentioned. With the clinical data incomplete we cannot prove this Case 6 to have been one of "primary renal gout," but we believe that it may represent such an entity.

All 6 of our cases, except Case 5, showed moderate to marked benign nephrosclerosis. In Case 5 the nephrosclerosis was slight. All previous pathological descriptions have stressed the contracted granular kidney of nephrosclerosis or its synonyms as the lesion found in gout. Minkowski[10] considered most but not all cases comparable to typical nephrosclerosis. He, as well as other authors, mentioned the rather rare finding of normal kidneys in gout, though usually in early stages of the disease. Schnitker and Richter[2] reported that people with gout showed a higher incidence of vascular disease, hypertension and nephritis than controls of the same ages. In addition, the 31 per cent of their patients with gout and nephritis, though ten years younger than those without nephritis, demonstrated more arteriosclerosis. Thirteen of the 17 patients with nephritis had hypertension, the blood pressures averaging 180 systolic, 110 diastolic. Coombs[3] also found that arteriosclerosis seemed to occur earlier in patients with gout and believed that hypertension was probably secondary to renal damage. Talbott[9] stated that patients with gout tend to develop arteriosclerosis prematurely throughout the body. It may therefore be concluded that gout seems to predispose to early arteriosclerosis, which manifests itself in the kidney as nephrosclerosis. Hypertension, which is more common than in nongouty patients of the same age, may serve to accentuate the nephrosclerosis.

Case 1, which showed extensive pyelonephritis leading to death from uremia, focuses attention on this important cause of renal damage. In addition to marked scarring there were multiple abscesses, frequently with deposits of urates around or in the abscess (Fig. 5). In a recent paper Spitz et al.[15] report a similar case of gout, which showed acute pyelonephritis limited to areas of urate deposits. Case 6 in our series also demonstrated extensive healed and some chronic pyelonephritis, with occasional deposits of urates in small abscesses. In an additional case (Case 3), there were only occasional small bands of healed pyelonephritis, but several urate deposits could be found in the medulla at the apex of the scarred area (Fig. 4). Another case (Case 2) revealed multiple small areas of old inflammation only suggestive of pyelonephritis.

Thus, in our series of 6 cases, 2 showed extensive chronic pyelonephritis, and 1 showed definite but not significant healed pyelonephritis.

There was an apparent relation between many of these areas of pyelonephritis or abscess and the deposits of urates. The urates were frequently beside or in abscesses or in the medulla just beneath areas of pyelonephritis. The work of Mallory and his co-workers[16] stressed the role of urinary obstruction in pyelonephritis. Blockage of tubules by urates serves as a logical explanation for the development of pyelonephritis in the areas draining into these tubules.

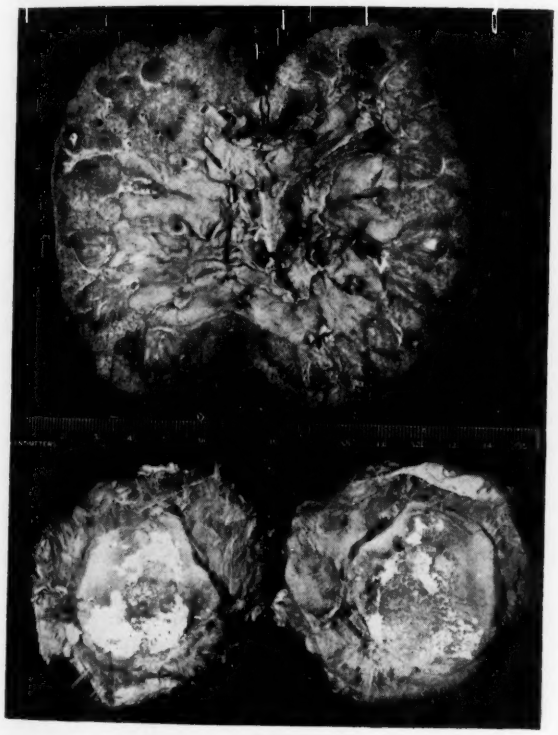

FIGURE 5. *Gross Changes in the Kidney and Knee Joint in Case 1.*

Reference to the literature reveals few descriptions of pyelonephritis in gout. Talbott[9] mentions a case, and Spitz et al.[15] recently reported the case referred to above. It may be that the older descriptions do not differentiate healed or chronic pyelonephritis from vascular nephritis. Certainly, since the work of Weiss and Parker,[17] the distinguishing features of pyelonephritis, especially the healed variety, have been more clearly understood and more frequently recognized.

We can only conjecture about the effect on the kidneys of transient or persistent elevations of uric acid levels in the blood and of the increased excretion in some cases. Transient albuminuria during attacks is frequent, and Talbott believed that there may be renal damage secondary to prolonged and excessive excretion of uric acid. Folin[12] demonstrated in all animals studied that urates were stored only in the kidneys, probably preliminary to excretion. He observed temporary renal impairment in dogs after injections of large quantities of urates. In addition, 2 patients with gout had temporary rises in nonprotein nitrogen levels after the injection of urates. This did not occur in nongouty subjects.

SUMMARY

A detailed study of the kidney pathology in 5 proved cases and 1 unproved case of gout is presented because of the frequency of renal dysfunction accompanying this disease. All kidneys showed significant or marked benign nephrosclerosis and deposits of urates in the medulla, probably originally in the collecting tubules. These findings conform to previous studies. One case showed kidney changes typical of gout but no clinical or joint manifestations of the disease and may have represented "primary renal gout."

In addition to these findings, 2 cases showed marked pyelonephritis, and 1 of these patients died in uremia. In another case there were small focal areas of healed pyelonephritis, and a fourth case suggested this. There was a frequent association between tubules blocked by urates in the medulla and abscesses nearby or pyelonephritis in the cortex above. It is suggested that tubular blockage by urates predisposes to pyelonephritis, which may contribute to the renal damage commonly observed in gout.

We are indebted to Miss Lillian Leavitt for the special stains and to Mr. Leo Goodman for the photography necessary for this study.

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PLEURAL-FLUID EOSINOPHILIA*

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PLEURAL-fluid eosinophilia has occurred rarely enough to be an unfamiliar phenomenon but frequently enough to have been the subject of considerable speculation about its diagnostic and prognostic significance. Since eosinophils are uncommon in the usual cytology of pleural fluid, the presence of any might be considered as representing a significant eosinophilia. For the purposes of this discussion, however, pleural-fluid eosinophilia is considered to be present when over 5 per cent of the cells in an effusion are eosinophils. Ever since Widal and Ravaut[1] first called attention in 1900 to the value of the cytologic study of thoracic fluid, pleural-fluid eosinophilia has been found in association with tuberculosis, convalescent lobar pneumonia, Löffler's syndrome, asthma and many other conditions. Many cases were described at a time when bacteriologic and roentgenologic confirmation of diagnoses was not possible. It is probable that some would be placed in more exact categories today. The diseases that have been associated with pleural-fluid eosinophilia are listed in Table 1.

Because of the frequency with which any pleural effusion is identified with tuberculosis, the significance of an eosinophil-containing effusion in relation to this disease should be carefully considered. If it were often, or even occasionally, the first evidence of pulmonary tuberculosis, it would naturally assume the same significance as an effusion containing predominantly lymphocytes. In all cases in the literature that have come to our attention, however, the effusion has been associated with tuberculosis, not as one of the early manifestations but late in the course of the disease.

In Clarke's[2] case, in which tubercle bacilli were isolated from the eosinophil-bearing effusion by animal inoculation, the patient had fever and roentgenologic evidence of numerous pulmonary infiltrations. The patient of Pratsicas and Antoniou[3] was already suffering from both pulmonary tuberculosis and Addison's disease at the time that the pleural-fluid eosinophilia was discovered. Diagnoses were confirmed at autopsy. Gill's[4] patient had peritoneal tuberculosis, proved by laparotomy and biopsy, but pulmonary parenchymal involvement was not demonstrated roentgenographically, probably because of massive pleural effusion. At autopsy, however, eight weeks later, pulmonary disease was found. Several other cases were reported prior to the general use of roentgenograms, but the signs and symptoms at the time of discovery of pleural-fluid eosinophilia left little doubt about the underlying tuberculous pulmonary disease. Two had unequivocal pulmonary signs[1, 5]; 2 others had marked cough, fever and weight loss[6]; and another had concomitant tuberculous peritonitis.[7] The eosinophil count in cases of tuberculous pleural effusion has varied from 5 to 80 per cent.

In one other connection an eosinophil-containing effusion may be an occasional accompaniment of tuberculosis. The fluid that sometimes accumulates after artificial pneumothorax has been found to contain a high percentage of eosinophils. Schwartz and Broadbent[31] frequently fluoroscoped tuberculous patients after initial artificial pneumothorax and aspirated fluid at the time of earliest evidence of fluid accumulation. Of 7 patients who accumulated fluid, 6 had 64 to 90 per cent and the seventh had 13 per cent eosinophils. In all cases the blood eosinophil count was only 4 to 7 per cent, and the fluid disappeared within a few weeks. Two other tuberculous patients, without pneumothorax, were tapped at the onset of pleural effusion, and in neither did the fluid contain significant numbers of eosinophils. Other cases of pleural-fluid eosinophilia are reported in patients who have had pneumothorax for several months.[32]

At least a dozen times, pleural-fluid eosinophilia has been reported in patients with the clinical manifestations of bacterial pneumonia, with lobar distribution and pneumococci in the sputum.[10, 11] In 1 case the organism was actually grown from material obtained by needle puncture of the affected lobe.[10] In these cases, with only 1 exception, the effusion did not appear until the tenth day of the illness. The greatest number of eosinophils was usually observed around the twentieth day. Blood eosinophilia was present in all cases, but was only of moderate degree, and never equaled the degree of pleural-fluid eosinophilia.

As might be expected, conditions in which pulmonary infiltrations are associated with blood eosinophilia, such as Löffler's syndrome, occasionally give rise to an eosinophil-containing pleural effusion. Löffler[37] himself reported that some of his cases showed pleural involvement, as evidenced by pleural pain and friction rub. Roentgenograms

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also revealed small pleural effusions, which were as fleeting as the pulmonary infiltrations themselves. In fact, they were so small and so transient that thoracentesis was not attempted. It remained for Nagel,[22] in 1941, to report the first case of Löffler's syndrome associated with pleural-fluid eosinophilia. The effusion, on the left, consisted of several hundred cubic centimeters with an eosinophil count of 82 per cent. Although the pulmonary infiltrations disappeared within a week, it was six weeks before the fluid was completely resorbed. Baumann[23] reported another case, in which the effusion was bilateral. In this patient the blood, the bone marrow and the pleural fluid showed marked eosinophilia. Ascaris ova were found in the stools, and though the pulmonary manifestations cleared spontaneously, it was not until after vermifuge therapy that the blood eosinophilia subsided. In this case, also, the infiltration disappeared before the fluid.

Although the mechanism of Löffler's syndrome is unknown, Löffler and others suspect that the condition is an allergic response to any one of several antigens. It has been found in patients infested with a variety of parasites, such as amebas,[38] *Ascaris lumbricoides*[39] and *Fasciola hepatica*.[40] A seasonal incidence was reported in China by Engel,[41] who found that cases appeared in May and June, during the pollination period of the privet bush. Most of Löffler's[37] cases in Switzerland occurred in July and August. If one accepts the suggestive evidence that these phenomena are a form of hypersensitive response, it is not too much to suppose that eosinophilic pleural reaction, with or without pulmonary infiltration, is occasionally a similar effect. The case of an asthmatic woman has recently been reported whose asthma disappeared with the onset of an illness characterized by pneumonitis, pericarditis, blood eosinophilia and eosinophilic pleural effusion.[20] Coincidentally, with the administration of tripelennamine hydrochloride (Pyribenzamine), the fever and effusion subsided and the asthma returned. Moreover, in a series of 16 cases of asthma with blood eosinophilia and transient pulmonary lesions by roentgenogram, 8 patients developed sterile pleural effusion in which marked eosinophilia was demonstrable.[21]

Why the pleura should respond with eosinophilia to such a wide variety of unrelated diseases (Table 1) is not clear. The erythrocytic content of most of these exudates has been high, and yet a third contained a minimal number of red blood cells. Most of these exudates have been of long standing, but there are exceptions, such as the effusions in cases of tuberculosis, immediately after initial pneumothorax. In general, there has been an associated blood eosinophilia, but in an occasional patient, both blood and bone marrow have lacked eosinophilia.[28] Tubercle bacilli have been isolated from several such effusions, but in none have other pathogenic organisms been found. In short, no universal common denominator is apparent. From the many conditions with which it has been associated, it is evident that pleural-fluid eosinophilia implies no specific etiology. It can be said, however, that the majority of such effusions have been benign and transient, with rapid recovery. Recently, the opportunity to study 3 patients with eosinophil-containing pleural effusion presented itself. In 1 case the effusion followed lobar pneumonia. In a second, although no precise etiology was established, there was a background of allergic disease.

TABLE 1. *Diseases Associated with Pleural-Fluid Eosinophilia.*

DISEASE OR CONDITION	NO. OF CASES
Infection:	
Tuberculosis[1-9]	10
Lobar pneumonia[5, 10-16]	13
Typhoid fever[2, 13]	2
Syphilis[5, 17]	2
Septicemia[5, 14, 18, 19]	4
Hypersensitivity:	
Asthma[20, 21]	9
Löffler's syndrome[22, 23]	2
Neoplasm[5, 24]	2
Traumatic hemothorax[5, 12, 25-27]	5
Unknown[1, 5, 6, 12, 25, 28-30]	11
Miscellaneous:	
Artificial pneumothorax for pulmonary tuberculosis[31, 32]	9
Bacterial endocarditis[33]	1
Bright's disease[5, 6, 29, 34]	7
Bronchitis[29]	1
Cardiac insufficiency[35]	1
Gangrene of lung[6, 8]	2
Infarct of lung[5, 14]	2
Pleuropericarditis[12, 20]	2
Polyarthritis[5, 6, 8, 12, 34, 36]	6

A third case, under the care of Dr. Louis K. Alpert, and included with his kind permission, was associated with Hodgkin's disease.

CASE REPORTS

CASE 1. A 36-year-old Negro was admitted to Mt. Alto Veterans Administration Hospital on April 16, 1949, because of cough and diarrhea of 5 days' duration. In the Army, he had spent 8 months on Okinawa, where he had suffered frequent bouts of mild diarrhea. Since then he had had occasional periods of 2 or 3 days when his bowels moved four or five times daily, and were loose but contained no blood, pus or mucus. Usually, however, the stools were normal in number and consistence. Two weeks before admission, diarrhea began, and 9 days later he had nausea and abdominal cramps. He had as many as fifteen loose green stools daily, none of which contained blood. There was also malaise, weakness and cough productive of foamy, mucoid sputum. These symptoms persisted until admission.

Physical examination revealed tachypnea and dehydration. There were signs of consolidation in the right lower lobe. Peristalsis was increased. The tip of the spleen was palpable, but the liver was neither enlarged nor tender to compression or vigorous percussion.

The temperature was 101.2°F., rising in a few hours to 105°F.

Roentgenograms confirmed the presence of right-lower-lobe pneumonia. The white-cell count was 22,000, with 83 per cent neutrophils, but no eosinophils were noted. Urinalysis was normal except for a faint albuminuria, which subsided with the fever. The blood Kahn test was negative.

Cultures of the sputum, blood, nasopharyngeal secretions and stools revealed no pathogens. Sigmoidoscopic examination disclosed a normal rectal mucosa. Repeated stool examinations failed to demonstrate any ova or parasites. A barium enema at a later date was normal. A purified protein derivative tuberculin test was weakly positive in the second-test strength. A cold agglutination test, Frei test and agglutinations for typhoid, para-typhoid, brucella and tularemia were negative. A skin test for trichinella and a complement-fixation test for amebiasis and echinococcosis were negative. Smear and culture of two collections of sputum and two gastric washings revealed no tubercle bacilli. Thymol turbidity and cephalin flocculation were within normal limits.

The diarrhea cleared rapidly within a few days and did not recur. On the 3rd hospital day (8th day of cough) the fever being unabated, 300,000 units of penicillin was given in aluminum monostearate. This dose was repeated 2 days later. The temperature fell to normal, but on the day after the second injection, the patient complained of burning of the eyes, and conjunctivitis ensued, persisting for 1 week. On the 7th hospital day, a blood eosinophilia (8 per cent) was found for the first time. On the 10th hospital day a roentgenogram showed marked resolution of the pneumonia. On the 11th day the patient complained of pain in the right side of the chest, and for the next week a pleural rub was audible and usually palpable. On the 18th hospital day roentgenograms showed a small right-sided pleural effusion. On the 24th hospital day thoracentesis yielded 70 cc. of a slightly opaque, reddish-brown fluid with a specific gravity of 1.021 and a protein content of 4.5 gm. per 100 cc. There were 40,000 erythrocytes per cubic centimeter and 30,000 other cells, of which 40 per cent were eosinophils, 38 per cent neutrophils, 5 per cent mesothelial cells, 7 per cent histiocytes and 10 per cent unidentified cells. Examination of sediment by the Papanicolaou technic demonstrated no malignant cells. No pyogenic organisms or tubercle bacilli were revealed by smear or culture. Two days later the blood eosinophil count was 22 per cent. The sputum contained no eosinophils. A roentgenogram on the 31st hospital day showed a minute amount of fluid remaining in the right pleural space. The blood eosinophil count on this day was 13 per cent. On the 34th day, it had subsided to 2 per cent. In an effort to determine the role of penicillin in the course of the disease, the patient was given a penicillin skin test and then a dose of 100,000 units of penicillin in aluminum monostearate, intramuscularly, to neither of which was there general or local reaction. He was discharged on June 6, 1949. He was re-examined in January, 1950, after having been in good health during the interval. Auscultation of the chest revealed a few rhonchi on the right, but a chest film was normal. A complement-fixation test for toxoplasma was negative.

CASE 2. A 32-year-old female interior decorator was seen because of pain in the left lower portion of the chest. During September and October, 1948, she noticed fatigue after her usual daily activities. Weight and appetite were unaffected. On November 13, she experienced pain in the left lower portion of the chest, intensified by deep breathing or any motion of the chest. There was also discomfort at the tip of the left shoulder, the left side of the neck and the left upper arm. There was neither fever nor night sweats. During the preceding year there had been a slight cough productive of a small amount of nonodorous, yellow, white, stringy sputum, attributed to heavy smoking. It had not changed in character or amount during the present illness.

The patient had had hay fever as a child while living in New York City, but had had no other allergic manifestations. Her mother had "pleurisy" in 1940 and 1948, but roentgenograms of the chest were normal. There was no history of contact with known tuberculosis.

Physical examination disclosed a patient who did not appear ill. The only positive findings were signs of pleural fluid on the left and a small uterine fibroid. A roentgenogram of the chest showed fluid just obliterating the left costophrenic angle and curved linear pleural opacities in the third and fourth left anterior interspaces.

The temperature was 98.8°. The pulse, respirations and blood pressure were normal. Urinalysis and a hemogram were normal. The sedimentation rate was 0.7 mm. per minute (Rourke–Ernstene method), normal being 0.4 mm. per minute. The tuberculin tests using P.P.D. (purified protein derivative), first and second strength, were negative.

The patient remained at home on modified bed rest, the symptoms subsiding promptly without medication. The temperature remained normal, and the sedimentation rate returned to normal in 1 week. Roentgenograms of the chest showed a complete resorption of the fluid during the next 3 weeks. The curved linear opacities originally present were no longer seen. The diaphragm was slightly elevated, and the left oblique film showed a 2-mm. thickening of the pleura along the left lateral aspect of the thorax. A double dose of second-strength P.P.D. (0.01 mg.) was negative.

She remained well except for slight evening fatigue until January 24, 1949, when there was a recurrence of pain in the left side of the chest. The pain was milder than during the previous episode. Physical examination and a roentgenogram revealed even more pleural fluid on the left than previously. She was hospitalized at the George Washington University Hospital, where a thoracentesis yielded 75 cc. of serosanguineous fluid with a specific gravity of 1.020 and a total protein of 4.4 gm. per 100 cc. It contained 125,000 erythrocytes and 6500 leukocytes per cubic millimeter. A methylene-blue stain showed most of these to be lymphocytes, and it was not until a cell block was stained in a search for malignant cells that it was noted that there were also numerous eosinophils. No neoplastic cells were seen. Cultures of the effusion for pyogenic organisms and tubercle bacilli yielded no growth. Nasal smears and sputum contained no eosinophils. Three gastric aspirations revealed no tubercle bacilli by smear and culture. A tuberculin test using O. T. (Old Tuberculin) in 5-mg. and 10-mg. doses, five and ten times the usual second-test strength dose, were negative. In the stools no ova or parasites were found. The total eosinophil blood count was 750 per cubic millimeter. After the 2nd hospital day, the chest pain disappeared, and the patient remained asymptomatic thereafter. At the time of discharge on the 16th hospital day, no fluid was visible on a roentgenogram. One week after discharge, the sedimentation rate and blood eosinophil count were normal. During the ensuing year she was entirely well, and a roentgenogram showed only slight thickening of the pleura in the left oblique projection.

CASE 3. A 43-year-old housewife was admitted to George Washington University Hospital on April 26, 1949, complaining of shortness of breath, headache, swelling of the ankles and enlargement of the cervical lymph nodes of 6 weeks' duration. Two weeks previously, two cervical masses had been biopsied at another hospital, revealing a normal lymph node and normal salivary gland.

Physical examination on admission revealed enlarged cervical lymph nodes, including a mass, 2 by 4 cm. in diameter, below the right mandibular ramus and another, 1.5 by 1 cm. in diameter, above the inner third of the left clavicle. These were firm and movable. There were also signs of cardiac decompensation such as dyspnea, cyanosis, ankle edema, tachycardia, cardiomegaly and hepatomegaly and evidence of fluid at both bases.

A film of the chest showed an enlarged heart and bilateral pleural effusion. The white-cell count was elevated to 21,600, of which only 3 per cent were eosinophils. A urinalysis, the hemoglobin level and the blood urea nitrogen level were normal, and the blood Kahn test was negative.

The cardiac decompensation was treated successfully with digitalis and mercurial diuretics, so that the dyspnea, edema and liver size decreased markedly. As the patient improved, the cause of the underlying disease was sought, and several further abnormalities were brought to light. Severe headaches led to a lumbar puncture, revealing a pleocytosis of 20 leukocytes per cubic millimeter, of which 11 were polymorphonuclear and 9 lymphocytes, and an increase in spinal-fluid protein to 420 mg. per 100 cc.; the sugar was 110 mg., and the chloride 695 mg. per 100 cc., and the Kolmer test was negative. The white-cell count remained consistently elevated, between 20,000 and 30,000. The serum albumin-globulin ratio was abnormal, with 3.2 gm. of albumin and 3.3 gm. of globulin per 100 cc.

A P.P.D. tuberculin test was positive in the second-test strength. Agglutination tests for typhoid O and H, paratyphoid A and B, *Proteus OX19*, *Brucella abortus*, tularemia and heterophil antibodies were all negative.

During the whole of the hospital stay, bilateral pleural effusions continued to accumulate despite frequent thoracenteses. A typical specimen consisted of 500 to 1000 cc. of pale-yellow fluid with a specific gravity of 1.018 and protein content of 3.8 gm. per 100 cc. In several of these specimens, tubercle bacilli were sought in vain by smear, culture and guinea-pig inoculation. The first thoracentesis was performed on the 9th hospital day, and revealed 1800 leukocytes per cubic millimeter, of which 80 per cent were lymphocytes and only 1 per cent eosinophils. An eosinophilic pleural effusion first appeared on the 17th hospital day, when the fourth thoracentesis revealed 8600 leukocytes per cubic millimeter, of which 60 per cent were eosinophils, 23 per cent neutrophils, and 17 per cent lymphocytes. Another thoracentesis on the 31st day demonstrated 37 per cent eosinophils. It is noteworthy that frequent differential counts of the blood before, during and after the eosinophilic pleural effusion showed no blood eosinophilia, except for one count of 6 per cent on the 40th hospital day.

Finally, although two of the cervical masses had already been biopsied and found to be a normal lymph node and salivary gland, a third cervical mass was excised. Microscopical examination showed a lymph node with the typical pleomorphism, eosinophils, and Reed–Sternberg cells of Hodgkin's disease. A course of nitrogen mustard therapy was given, with only moderate improvement. Roentgen-ray therapy over the mediastinum, both cervical regions and the occipital region of the head gave further improvement, and the patient was discharged on August 18, 1949, to be cared for at home.

Discussion

In the attempt to establish the etiology of pleurisy with effusion, it is usual to consider tuberculosis as the most probable cause until proved otherwise. It is urgent, however, that specific efforts be made to implicate the tubercle bacillus. A simple and important first step should be the tuberculin test. Tuberculous pleurisy with effusion occurs in patients who usually have a high degree of hypersensitivity to tuberculoprotein. A negative test, therefore, virtually excludes tuberculosis except in those who are extremely ill or dehydrated or have a complicating exanthematous infectious disease; tuberculosis may be present in them despite a negative tuberculin test. A positive tuberculin test, on the other hand, does not establish the tuberculous nature of the effusion, but makes it mandatory that an intensive search be made for the tubercle bacillus in the effusion.

Such a search was made in all the patients described above, and tubercle bacilli were not discovered. Moreover, in Case 1 the lobar distribution in a lower lobe and the transitory course would be unusual for tuberculosis. The tuberculin test was only weakly positive in the second-test strength during convalescence, at a time when a patient with tuberculous effusion would be expected to react strongly to tuberculoprotein. In Case 2 the lack of response to 10 mg. of O. T. seems to exclude a tuberculous etiology.

The abnormality in Case 1 was unlike the usual Löffler syndrome in at least two respects — namely, the lobar distribution and the presence of pulmonary infiltrations before the development of blood eosinophilia. Moreover, tests for infection with trichinae and echinococci were negative. In Case 2 blood eosinophilia was noted, but pulmonary infiltrations were not found. It may be that pulmonary involvement was transient and had disappeared at the time the eosinophil-containing effusion was discovered; this occurred in the later stages of the cases reported by Nagel[22] and Baumann.[23] Though this patient's illness was not consistent with the usual findings in Löffler's syndrome, the response was possibly due to some related hypersensitivity phenomenon. The past history of allergy offers some support for this supposition.

The conjunctivitis that developed several days after the administration of penicillin in Case 1 suggests drug sensitivity as the cause of the eosinophilia in blood and pleural fluid. Blood eosinophilia after the administration of penicillin in oil and wax has recently been reported.[42] The fact that the patient in Case 1 showed no demonstrable reaction to a preparation of penicillin similar to that which he had originally received cannot rule the drug out as a possible exciting antigen, since penicillin sensitivity is variable in the same person at different times.[43] Nor was there any positive proof that the drug was responsible, and the role of penicillin in this case must remain an open question.

Lobar pneumonia, on the other hand, has frequently caused such a chain of events as occurred in this case. Blood eosinophilia has been noted in the convalescent phase of acute infectious diseases in general and lobar pneumonia in particular.[44] In view of the recent discovery that stimulation of the adrenal cortex with pituitary adrenocorticotrophic hormone (ACTH) leads to a decrease in circulating eosinophils,[45] it is conceivable that the eosinophilia following acute infections is a rebound phenomenon after adrenocortical stress. Sterile eosinophil-containing pleural effusion has followed lobar pneumonia in at least 12 reported cases. It is our opinion that Case 1 probably belongs to this group.

In Case 3 the pleural fluid was probably caused by involvement of the mediastinum by Hodgkin's disease. Of 174 cases of Hodgkin's granuloma studied by Jackson and Parker,[46] pleural effusion developed during the illness in 23. Some of these effusions were serous, some sanguineous, and 1 chylous, but in none was a significant eosinophilia discovered. Case 3 is unique, since a similar phenomenon in association with Hodgkin's disease has never previously been described, to our knowledge. It serves as a reminder that eosinophil-containing pleural ffuid is not always associated with benign conditions.

Pleural-fluid eosinophilia has taken on added importance since the reawakening of interest in the diagnosis of neoplasm from the cytologic study of all human fluids, including pleural effusions. It may be expected that as the procedure becomes more prevalent, a corresponding increase in eosinophil-containing effusions will be discovered. As in

Case 2 probably many cases missed by the technician will be found by the pathologist.

Summary

Three cases of eosinophil-containing pleural effusion are presented, including the first reported case in association with Hodgkin's disease. It is emphasized that the phenomenon may follow lobar pneumonia or may accompany Löffler's syndrome, asthma or obvious pulmonary tuberculosis, but no case in which it was the first sign of tuberculosis has been reported to our knowledge. The vast majority have been mild and transient with complete recovery. It is expected that as more pleural effusions are studied cytologically, more eosinophil-containing fluids will be found.

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PLASMACYTOMA OF LYMPH NODE*

Report of a Case with Multiple Myeloma

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IN A comprehensive review of 127 extramedullary plasmacytomas in 1943, Hellwig[1] found only 4 cases in which plasmacytoma appeared to originate in lymph nodes. Search of the subsequent literature reveals only a single additional example.[2] Because plasmacytoma of lymph nodes may be associated with grave prognostic significance, the case presented below, which was followed for three and a half years, is considered worthy of comment.

CASE REPORT

A 52-year-old man entered the hospital on June 27, 1946, because of a painless swelling in the right inguinal region of 4 weeks' duration. Except for a history of phlebitis of the right leg 1 year before, the past history was noncontributory, and he had no other complaints.

Physical examination revealed a hard, discrete, slightly tender mass the size of a small walnut over the medial aspect of the right thigh 3.8 cm. below the inguinal ligament. The liver and spleen were not palpable, and no other lymph-node enlargements were present.

The urine showed a specific gravity varying from 1.009 to 1.026, and upon one occasion, a faint trace of albumin was noted. Microscopically, no abnormal findings were reported. A hemogram demonstrated a red-cell count of 5,750,000 and a white-cell count of 10,500, with 6 per cent stab forms, 56 per cent neutrophils, 5 per cent eosinophils, 26 per cent lymphocytes and 7 per cent monocytes. The corrected sedimentation rate was 40 mm. per hour (Wintrobe method). A coagulogram showed a moderate prolongation of the prothrombin time. The blood Kline test was negative.

On June 28, under local anesthesia, a well demarcated lymph node was removed and sent for pathological study.

On macroscopic examination the specimen consisted of an enlarged lymph node, which measured 4 by 2.5 by 2.2 cm. It appeared to be completely enclosed by a thin, fibrous capsule. On section, the cut surface presented a gray, smooth, moist appearance.

Microscopical examination showed the lymph node to be extensively infiltrated by a uniform type of cell, which resembled adult, well differentiated plasma cells. These cells lay in solid sheets with very little recognizable stroma; the nuclei were eccentric in position, with coarse and peripherally arranged chromatin giving many nuclei a typical "cartwheel" appearance. The cytoplasm was abundant and pink staining, but no Russel bodies could be identified. With the diffuse infiltration of the lymph node by plasma cells, there still remained within the periphery distinct follicles containing secondary nodules that were surrounded by thin, condensed layers of small lymphocytes. In some situations a thin layer of small lymphocytes was noted in the periphery of the node. The capsule was thin and did not appear to be invaded by cells. The diagnosis was extramedullary plasmacytoma of the lymph node.

The diffuse infiltration and enlargement of this node by cells bearing a striking resemblance to plasma cells (Fig. 1) with selective sparing of the follicular architecture was remarkable. The prognosis in this case was guarded. It was suggested that the patient have bone-marrow studies, total protein determination, search for Bence–Jones or other abnormal proteins in urine and blood and x-ray examinations of the bony skeleton for evidence of multiple myeloma and of the chest for evidence of enlarged mediastinal lymph nodes.

He was discharged from the hospital on July 2. Early in August, x-ray films of the ribs, long bones and skull failed to reveal any pathologic changes. The urine showed no Bence–Jones protein, but bone-marrow studies and blood protein studies were not carried out. He received irradiation to the right inguinal and iliac regions.

About 1 year later he was again seen because of slight recurrent swelling in the right inguinal region. Permission for another biopsy was refused, and he was lost track of for 2 years.

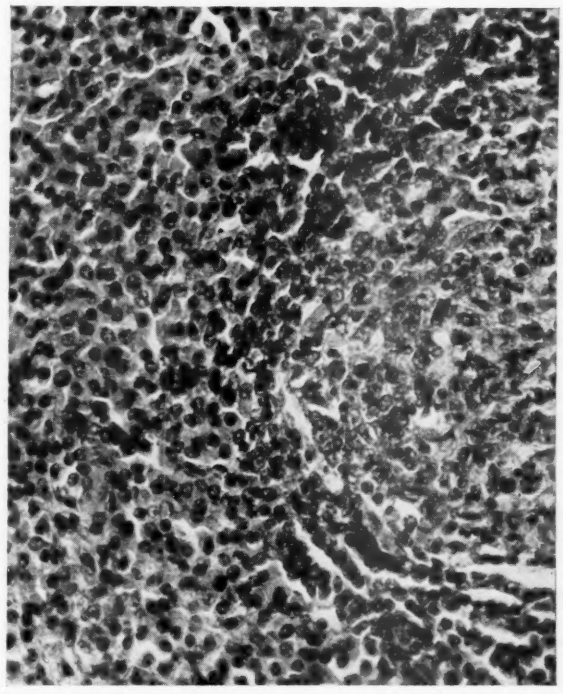

FIGURE 1. *High-Power Photomicrograph (x360), Showing the Germinal Center at the Right, with a Thin Surrounding Layer of Lymphocytes and a Typical, Regular Plasma-Cell Infiltrate at the Left.*

In September, 1949, the patient complained of discomfort in the upper abdomen and pain in the chest. At this time Bence–Jones bodies were demonstrated in the urine. X-ray films taken a few days later revealed an area of destruction in the ninth rib on the right, compatible with a diagnosis of myeloma. X-ray study of the pelvis and skull showed no bony changes. The blood chemical findings at this time were as follows: nonprotein nitrogen, 23.0 mg., calcium 10.4 mg., and total protein 6.81 gm. per 100 cc., with an albumin of 4.75 and a globulin of 2.06 gm. per 100 cc. On the same day sternal bone-marrow puncture revealed 11.5 per cent plasma cells and 2.5 per cent plasmablasts in a differential count. The following comment was added to the hematologic report:

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Although the number of plasma cells does not indicate the presence of a focal lesion of plasma-cell myeloma at the site from which this marrow was aspirated, the character of the plasma cells and plasmablasts, as well as the increase in numbers, definitely establishes a diagnosis of plasma-cell myeloma. In some areas, focal collections of plasma cells indicate greater infiltration than would seem apparent from the differential count.

On October 14 the patient experienced severe pain in the left side of the chest and left arm. X-ray examination revealed pathologic fractures of the ninth and tenth ribs in the posterior axillary line on the left, with many vacuolated and honeycombed areas of rarefaction within the upper third of the left humerus immediately below the surgical neck (Fig. 2), as well as similar lesions in the inferior angle of the left scapula. These findings were interpreted as characteristic of multiple myeloma. The patient then went to New York City, where the diagnosis of multiple myeloma was corroborated by Dr. I. Snapper.

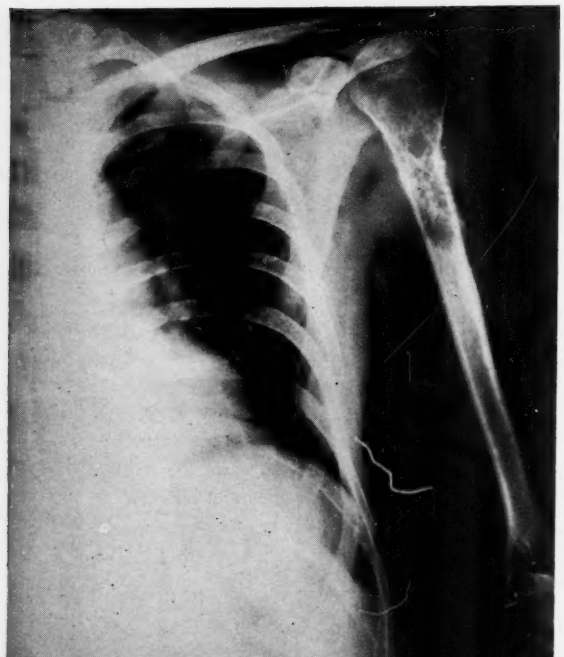

FIGURE 2. *Roentgenogram of the Left Side of the Chest and Left Shoulder Taken Three and a Half Years After Biopsy. Note the pathologic fractures of the ninth and tenth ribs, the classic "moth-eaten" lesion in the upper third of the left humerus and the honeycombed appearance of the inferior angle of the left scapula.*

The patient ran a progressively down-hill course characterized by increasing renal failure with marked albuminuria and Bence–Jones protein in the urine. On repeated occasions, plasma cells in large numbers were demonstrated in the sternal bone marrow, and x-ray examinations showed new lesions in the ilium. He died on May 3, 1950, 47 months after lymph-node biopsy.

Autopsy disclosed massive involvement of the retroperitoneal, periaortic and mediastinal lymph nodes, which showed complete replacement of lymphocytes by plasma cells, the majority of which were typical although occasional giant and multinucleated forms were encountered. These plasma cells occurred in broad sheets with very little supporting stroma.

The bone marrow of ribs, sternum and humerus was almost completely replaced by solid masses of plasma cells. The kidneys showed plugging of the majority of tubules by polychromatic albuminous casts, but no amyloid could be demonstrated.

Discussion

Plasmacytoma in its classic form is largely limited to bones, and yet extramedullary plasmacytomas have been described in numerous situations throughout the body.[1] This is not surprising in view of the ubiquitous nature of the plasma cell and the generally accepted belief that plasma cells arise from the same stem cell as the small and medium-sized lymphocytes. If this accepted belief is true, what is more surprising is that so few cases are recorded in which plasmacytomas appear to arise in lymph nodes.

Of the 4 cases classified by Hellwig[1] as plasmacytomas arising in lymph nodes, the case of Basset and Scapier[3] is open to doubt, for the description of the original tumor removed from the neck gave no indication of the removed tissue other than to state that the tumor was malignant. Subsequent resection of the irradiated portion of the sternocleidomastoid muscle showed an indurated tumor mass. The microscopical description of this lesion gave no indication of residual or recognizable lymph-node architecture.

The case of Maresch, cited by Hellwig,[1] indicates that full-blown myeloma lesions were already present in the vertebras, humerus and femur, as well as being generalized in other lymph nodes at the time the mass in the neck was resected. The fact that a small tumor had been present for fifteen years is suggestive but not conclusive that a plasmacytoma had arisen in a lymph node at this site and remained quiescent for fifteen years, and had then become generalized.

Cases 2 and 3 of Jackson, Parker and Bethea[4] may possibly be acceptable as plasmacytomas arising in lymph nodes. In Case 2 classic plasmacytoma was found in the lymph node of the neck. Although the patient complained of pain in the left hip that had been present for "some time," x-ray films at the time of removal of the node failed to show lesions of bone in this region. Only two months later were circular areas of bone destruction noted in the left iliac crest and left femur. No Bence-Jones proteins were present in the urine until five months after biopsy. Although no autopsy was obtained, it is unlikely that this case was anything but an acceptable example of multiple myeloma. Case 3 revealed a plasmacytoma of a lymph node behind the left ear. X-ray studies of the bones were negative, and no Bence-Jones proteins were present in the urine. This patient was followed for three years and was always without signs or symptoms of multiple myeloma. This short period does not, of course, exclude the possibility of subsequent dissemination.

Jequier-Doge, Nicod and Chapuis[2] reported the case of a twenty-five-year-old man in whom routine x-ray study of the chest in the Army revealed a solitary, left mediastinal shadow. Investigation disclosed a slightly elevated sedimentation rate and a serum protein varying between 10 and 11 gm. per 100 cc. The urine was negative for Bence-Jones protein, and sternal puncture revealed only 2 plasma cells per 100 white blood cells. X-ray examination of the bones was negative.

Four or five years later, the patient began to lose weight and strength. The x-ray shadow of the left mediastinal mass had not altered. Sternal puncture showed between 22 and 23 per cent plasma cells in the marrow. Shortly after, the urine contained Bence-Jones protein. In the sixth year of follow-up study the patient demonstrated tuberculosis of the left lung, with dissemination to the right side. No change was noted in the left mediastinal mass. Sternal puncture revealed 11 per cent plasma cells. A few months later the patient died.

At autopsy, the left mediastinal mass measured 6.5 by 6.0 by 2.5 cm. On section it was moist and dark red, with mottled gray but without caseation necrosis. It was surrounded by a continuous capsule, "which made one think that it had developed in a lymph node." Histologically, no lymphoid tissue was recognizable. The mass was composed of cellular areas suspended upon a fine reticulum and separated by dense fibrous septums. The cells comprising the mass were fairly large, with abundant homogeneous cytoplasm containing "cartwheel" nuclei. Many of the cells were altered but, in general, resembled plasma cells. Some of the cells were giant in size. No foci of caseation necrosis were present, and no invasion beyond the capsule was seen. No other mediastinal lymph nodes were involved. The sternum showed a diffuse infiltration by plasma cells. The lungs demonstrated bilateral, ulcerative tuberculosis. There was amyloidosis of the kidneys, spleen and adrenal glands.

Thus, of the 5 cases of plasmacytoma of lymph nodes heretofore reported in the literature, 2 (Cases 2 and 3 of Jackson et al.[4]) appear definitely to have been present in lymph nodes, whereas those of Maresch (cited by Hellwig[1]), Basset and Scapier[3] and Jequier-Doge and his associates[2] are presumptive but not proved to have involved lymph nodes. The case reported by McNamara and Rogers[5] was undoubtedly a metastasis from a primary plasmacytoma of the tonsil.

It is well known that bones may be affected by plasma-cell myeloma and at the same time not show any change in the bony structure on x-ray examination. Since, in the case reported above, as in Cases 2 and 3 of Jackson, Parker and Bethea,[4] no studies of the bone marrow or blood protein were done at the time of the initial resection of the lymph nodes, it is impossible to say whether the bone marrow was involved by myeloma, even though the x-ray films were normal. In Case 2 of Jackson et al.[4] x-ray evidence of multiple myeloma appeared two months after lymph-node resection. This suggests that the bones were probably involved at the time of lymph-node removal. In the case reported above, almost three and a half years elapsed before clinical manifestations of plasma-cell myeloma became apparent. This, however, does not definitely exclude the possibility that the bones were involved at the time of the lymph-node resection.

The histogenesis of the plasma cell is controversial, and a critical review of the voluminous literature on this subject is beyond the scope of this report. The bulk of the evidence, however, favors the view that plasma cells are ultimately derived from cells of the reticuloendothelial system, either directly or through an intermediate lymphocytic stage.[6-9] In small numbers, plasma cells appear to be normal constituents of bone marrow and lymph nodes. Therefore, plasmacytomas may arise and, indeed, could be primary in lymph nodes. The surprising fact, however, is that so few cases have been reported in which this seems to have been so.

The histologic appearance of extramedullary plasmacytomas, particularly in lymph nodes, gives no indication of their relative benignancy or malignancy or offers no clue to the clinical behavior of the disease other than to indicate that the eventual prognosis is exceedingly grave. In the case reported above, as in other cases of plasmacytoma of lymph nodes, the predominating cell was a uniform and more or less typical plasma cell without variations in size, shape or staining quality and without evidence of great mitotic activity.

According to Hellwig,[1] the location of the extramedullary plasmacytoma rather than its histologic appearance plays the more important part in prognosis. He believes that as long as the plasma-cell tumor is localized and confined to soft tissues, a clinical cure may be obtained by a combination of surgical removal and irradiation. Similarly, extramedullary plasmacytomas of the conjunctiva have distinctly non-neoplastic properties, whereas tumors of identical cytologic character in the air passages or tonsils may be highly destructive and may produce widespread metastases. On the other hand, once the tumor is present in the bones or lymph nodes, no known therapeutic measures, thus far, have prevented fatal outcome. Although Case 3 of Jackson et al.[4] showed no bony involvement three years after lymph-node biopsy, the time of follow-up study was too short to permit a conclusion that the patient was cured. A period of eight years may elapse between the first appearance of extramedullary plasmacytoma and generalized dissemination, as shown in Case 1 of Jackson and his coworker,[4] in which the primary site was a tonsil.

Plasmacytoma may arise in lymphoid structures and subsequently involve bone, or the converse may

be true. Therefore, plasmacytomas of lymph nodes might be interpreted in one of two ways: that the plasmacytoma is primarily extramedullary and is arising in the lymph node, or that the plasma cells in the lymph node are part of a generalized though not clinically apparent plasma-cell myeloma and are infiltrating the lymph node and compressing the follicles in a manner similar to that seen in leukemia. Multiple myeloma may occur with a blood picture of plasma-cell leukemia.[10, 11] This strongly suggests that multiple myeloma, like the lymphomas, is a neoplastic disease of multicentric origin. Under these circumstances, the only criteria for determining which site is primary rests largely upon clinical examinations and follow-up study. As Ghormley et al.[12] have shown, these various clinical examinations give inconstant results in any individual case, so that caution should be exercised before one decides that the evidence for disseminated myeloma is not present at the time a diagnosis of extramedullary plasmacytoma is made. In the case reported above, the evidence is suggestive but by no means conclusive that the primary site was the inguinal lymph nodes and that disseminated myeloma was not present at that time but occurred a number of years later.

Summary

A case of plasmacytoma of lymph node, the sixth in the literature, which was followed for three and a half years and then developed into fatal multiple myeloma, is reported.

It is possible that the disease originated in the lymph node and later became disseminated, but it is equally possible that the bone-marrow was involved at the time of lymph-node biopsy, without x-ray evidence of bone destruction.

In any event, plasmacytoma in lymph nodes carries a grave prognostic significance and is usually followed, after varying periods, by clinically manifest multiple myeloma.

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MEDICAL PROGRESS

CARDIAC CATHETERIZATION*

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CARDIAC catheterization is now a recognized and accepted procedure and has proved its great value both as a research tool in cardiovascular physiology and as a diagnostic aid in certain types of heart disease, particularly those of congenital etiology. This report discusses the technical aspects of the procedure and describes some of the accomplishments in diagnosis and research. No attempt will be made to summarize the literature completely.

Catheterization of the right side of the heart was first carried out in man by Forssmann,[1] who, in 1929, performed the maneuver on himself. A year later Klein[2] reported 11 successful cardiac catheterizations done for the purpose of obtaining mixed venous blood samples requisite to the measurement of cardiac output by the Fick principle. Two of these were catheterizations of the right ventricle confirmed radiographically. In 1932, under the stimulus of Klein's publication, Padilla, Cossio and Berconsky[3] made comparative studies on 3 patients of the indirect Fick principle with the direct Fick method by catheterizing the right auricle. Except for these two studies catheterization of the heart was employed[4-6] only as a procedure for angiocardiography until Cournand and Ranges,[7] in this country, reported application of the method to cardiac-output determination on 8 occasions in 4 patients. Although Lenègre and his associates[8] in France were simultaneously and independently exploring the possibilities of the procedure, the work of Cournand and Ranges appears to have launched the extended and continuous use that catheterization now enjoys as a method of research and diagnosis.

DESCRIPTION OF METHOD

The principle of the procedure of cardiac or venous catheterization is simple. A radio-opaque catheter, similar to a ureteral catheter, except that it has a built-in curve at its tip, ranging in size from No. 6 to No. 9, is inserted into the antecubital vein of either arm. The vein is usually first directly exposed through a small incision. The catheter is then guided, under fluoroscopic control, through the innominate vein into the superior vena cava. From there it can be advanced into the right auricle, the right ventricle and either pulmonary artery from its origin to one of its smallest divisions. In addition, the catheter tip can be directed down the inferior vena cava into a renal vein, into a hepatic vein, into the coronary sinus, or where openings exist between the right and left chambers of the heart it may also be guided into the left auricle, a pulmonary vein, the left ventricle or the aorta. It requires little imagination to appreciate the difference between the theoretical possibility of the accomplishment of these objectives and their realization in practice. However, with experience and careful technic, a skillful operator can attain his objective in a reasonably high percentage of cases.

Two types of investigation are then commonly carried out. The distal end of the catheter may be attached to an appropriate recording device, and a measurement made of the blood pressure that exists in the portion of the circulatory system where the tip of the catheter is placed. Blood can be drawn through the catheter and, with due precautions to prevent its exposure to air, can be analyzed for its oxygen content. In addition to these two procedures, the tip of the catheter can be converted into an exploring electrode and endocardial electrocardiograms recorded, and blood obtained from the coronary sinus can be analyzed not only for its oxygen content but also for other substances important in cardiac metabolism.

Several types of apparatus may be employed for the registration of blood pressure. The simplest, and the least accurate, is a water manometer. A method that has been and is still widely employed utilizes the principle of a light beam reflected from a mirror affixed to a movable membrane on an instrument known as a Hamilton manometer. Recently, electric methods of registering pressures, based for the most part on either the principle of the strain gauge or the condenser microphone, have been increasingly used. The latest development has been to devise a manometric sound that is located at the tip of the catheter.[9] Such an instrument, if it proves practicable, may diminish artefacts and errors in pressure registration due to the movement of the catheter as well as the damping effect of the long column of fluid in the catheter with its low frequency.

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Precautions and Hazards

Because of the dramatic nature of the procedure the authors of the early articles published were almost always at pains to emphasize its comparative safety and the lack of untoward consequences. The descriptions of their technics were frequently accompanied by statements of the number of catheterizations that had been performed without ill effects. Such statements were desirable at the time to establish the method as the legitimate medical procedure that it is. However, there has been such an overemphasis on the simplicity and safety of the method that comparatively untrained physicians, surgeons and radiologists have mistakenly thought that they could undertake it with success and impunity. There are real as well as potential hazards in the technic that are multiplied many times in the hands of untrained or careless operators. There are technical tricks that must be learned by proper training and experience; only experience, too, will give the requisite knowledge and judgment to permit the proper evaluation of results and to avoid the errors inevitably resulting from too little knowledge. It is our opinion that cardiac catheterization should only be carried out in laboratories that are adequately equipped and by operators who have been fully trained under competent supervision.

With one exception,[10] the reported studies[11] of human beings who have died soon after catheterization have not shown lesions of the right side of the heart that might be attributable to this procedure, and some studies on animals[12] have also given negative results. Nevertheless, there are reports[13-15] of subendocardial hemorrhages, mural thrombi and small infarctions occurring in dogs killed at periods varying from a few hours to weeks after catheterization.

The occurrence of auriculoventricular nodal and ectopic ventricular beats and the development of ventricular conduction defects when the tip of the catheter is entering or in the right ventricle have been frequently observed and commented upon. This is well illustrated in the articles by Levine and his co-workers.[16, 17] These disorders of rhythm and conduction range from single ectopic beats to long runs of idioventricular rhythm, ventricular tachycardia and bundle-branch block. Rhythm disturbances of some degree will develop in almost every patient in whom the catheter is placed in, or passes through, the right ventricle. The abnormalities usually disappear promptly when the catheter tip is either advanced into the pulmonary artery or withdrawn into the right auricle, but we have observed persistence of bundle-branch block or of ventricular tachycardia for hours after complete withdrawal of the catheter. The obvious hazard is the development of ventricular fibrillation or standstill. This hazard is probably greatest in patients who already have irritable hearts or diseased or failing myocardiums; patients with marked coronary and rheumatic disease and fully digitalized patients fall into this group. Disturbances of auricular rhythm, developing when the tip of the catheter is in the right auricle, are much less common, but do take place. Ectopic auricular beats, auricular tachycardia and fibrillation have all been encountered. These, too, usually disappear when the position of the catheter tip is changed or removed from the auricle.

The danger of embolization from the procedure is not great. Air emboli to the periphery have been reported in patients with a right-to-left shunt in the heart; if they occur in the lungs in patients with normally closed cardiac septums, they are apparently innocuous. No published reports of emboli from dislodged thrombi either pre-existing in the heart or developing in the heart or venous system consequent to the procedure have come to our attention. However, pulmonary infarctions have been known to occur shortly after catheterization, especially in patients with auricular fibrillation.

Infection is a theoretical danger, but with proper aseptic technic and prophylactic use of antibiotics, this hazard should be infrequent. Venospasm in the arm may prevent manipulation of the catheter, and on rare occasions has necessitated surgical cut-down to permit withdrawal. Some patients may exhibit keloid formation at the incisional site.

Enough has been said to indicate that this procedure is not one to be undertaken casually or by the untrained. The technic, however, is one of great usefulness, and many thousand cardiac catheterizations have been done in this country and abroad with no ill effects. The reported or known number of occasions when serious consequences have occurred comprise a small handful, and even in this small group the complications were often attributable to the underlying heart disease and incidental to the technical maneuver. Nevertheless, to reduce the occurrence of untoward results to the minimum it is essential that certain rules be strictly observed: the entire procedure, from beginning to end, must be constantly monitored by a direct-reading electrocardiographic machine, such as a direct writer, a cardioscope or a cathode-ray oscillograph; and the tip of the catheter should not be allowed to remain in the right ventricle, except for the brief period necessary to obtain essential observations in that chamber. When disorders of the heart beat or rhythm occur the catheter should at once be withdrawn from the ventricle, and if they do not immediately disappear, the entire procedure should be terminated. If the patient is distressed or uncomfortable for no apparent reason, or if the operator is in any doubt about the wisdom of continuing the catheterization, it should be immediately abandoned. Suitable facilities for the handling of any circulatory emergency

should be immediately available. The duration of fluoroscopic observation should be held within a safe interval.

Obviously, a fully trained team of workers, operating with adequate equipment, is a requisite to the proper carrying out of cardiac catheterization.

A further aspect of the problem is the necessity of providing adequate facilities for the training of doctors who will use the technic diagnostically in clinical centers throughout the country. At the present time most of the laboratories where proper training can be obtained are chiefly concerned with the education of research investigators. The use of this procedure in clinical diagnosis is usually a sideline in these laboratories or is apt to be carried out elsewhere by men who have not had adequate training. This problem, as well as other phases of the whole question of cardiac catheterization, might well merit the consideration of a specially constituted committee, properly sponsored by an organization such as the Scientific Council of the American Heart Association.

Use in the Study of the Physiology of the Circulation

The employment of cardiac catheterization has greatly extended the field of knowledge in human cardiovascular physiology. Prior to its use there was comparatively little direct evidence concerning the physiology of the pulmonary circulation in man. What knowledge there was was based on inference from morphologic findings at post-mortem examination, from animal experimentation or from indirect studies. Now, within the space of eight years, knowledge of the pulmonary circulation in health and disease has been so enlarged that in some ways more is known about it than of the systemic circulation.

Pulmonary Pressure

The pioneer work in this regard is well summarized in an article by Cournand.[18] Here it is stated that the average pulmonary-artery pressure is 25 systolic, 8 diastolic, with a mean of 15. The reported findings of other workers, including ourselves, are in essential agreement with this.

Using an ingenious technic, Hellems, Haynes and Dexter[19] have been able to obtain a close approximation of pulmonary capillary pressure, by occluding a distal ramification of a small pulmonary artery by the tip of a catheter introduced in the usual manner through the heart. They report average values of 10 for the capillary pressure in normal man — a figure in general agreement with findings based on animal studies as well as levels found in the left auricle or pulmonary veins in patients with interatrial shunts.[20-24] Thus, it can be seen that the pressure gradient between pulmonary artery and capillary is only 5 or 6, testifying to low resistance in the normal pulmonary vascular bed.

Investigations[25, 26] of the response of pulmonary vascular pressures to exercise reveal that there is little or no increase in these pressures during moderate exertion in subjects with normal circulations, in spite of an elevated cardiac output, further evidence of the wide caliber and distensibility of the pulmonary vessels.

In certain patients with cardiac or pulmonary disease, the pressure in the pulmonary artery (or the systolic pressure in the right ventricle, which has the same significance) has been found to be elevated. This occurs in patients with failure of the left ventricle and with mitral stenosis.[25-29] In such cases the increase in arterial pressure is chiefly secondary to an increase in pulmonary capillary pressure transmitted back from an elevated left auricular pressure, as confirmed by determination of the pulmonary capillary pressure[28, 29] or direct measurements of the left auricular pressure in patients with mitral stenosis during operation.[28] Hellems et al.[29] have presented evidence, however, that when the capillary pressure in mitral stenosis exceeds a critical value, there is an added element of arteriolar constriction, resulting in further elevation of pulmonary-artery pressure.

Patients whose primary difficulty is pulmonary disease, particularly pulmonary fibrosis, may show an elevated right ventricular systolic and pulmonary-artery pressure that is secondary to changes in the pulmonary circulation itself.[26, 27, 30] Similar findings may occur in some patients with congenital heart disease. In such patients the pulmonary capillary pressure may be normal, and added evidence that this pulmonary hypertension is the result of pulmonary vascular disease is to be found in the reports of morphologic changes in the pulmonary vessels found at post-mortem examination.

Patients with pulmonary hypertension, of whatever etiology, usually respond to exercise or tachycardia with an increase in pulmonary pressure,[25, 26, 28] in contrast to normal persons. This may be due to a fall in output of the left side of the heart or to the fact that a failing left side of the heart or a stenotic mitral valve cannot accommodate itself to an increase in blood pumped by the right ventricle into an already distended pulmonary circulation, or it may be due to pulmonary vasospasm or to the fact that pulmonary vascular disease has made the pulmonary vascular bed rigid and nondistensible.

Much light has been thrown by such studies on the mechanism of dyspnea in heart failure and mitral stenosis and on the occurrence of strain and failure of the right side of the heart in pulmonary disease.

Although Cournand[18] himself has stated that clear-cut evidence of direct vasomotor effects on the lung circulation is lacking, he and his co-workers[31] have presented evidence for the potent effect of anoxia in increasing pulmonary arterial pressure,

which may be due to pulmonary vasoconstriction. It has been observed[32, 33] that experimental pulmonary emboli may result in great elevation of pulmonary-artery pressure, owing to widespread pulmonary vasoconstriction. The entire problem of the nervous and hormonal control of the pulmonary vessels and of the effect of drugs needs extensive elucidation.

Blood Flow

Cardiac catheterization has provided the means of obtaining the most accurate determination of cardiac output in man yet available, and has further made possible the determination of this output under varying conditions of stress and exercise and in heart failure that for the most part could not be obtained by the cruder, more indirect methods previously available.

The principle that underlies the estimation of the output was described originally by Fick and has been utilized in cardiac physiology for many years. If the total oxygen consumption of the body is determined and this figure is divided by the amount of oxygen given up by a unit quantity of blood in passing from the arteries to veins, the result is the total blood flow in the systemic circulation. In the past that part of this formula which it has been impossible to measure directly in man has been the oxygen content of venous blood that is a proper mixture of blood coming from all parts of the body. The only place where such mixture occurs is in the right side of the heart itself or the pulmonary artery. The cardiac output therefore is measured as follows:

$$\text{Cardiac output (in cubic centimeters per minute)} = \frac{\text{Oxygen consumption (cubic centimeters per minute)}}{\text{Systemic arterial oxygen content (vol. per cent)} - \text{pulmonary arterial oxygen content (vol. per cent)}} \times 100$$

The arterial oxygen content of blood from the right ventricle or right auricle can be substituted for that from the pulmonary artery but may be somewhat less accurate because of less uniformly complete mixing. Except in cases in which there is an abnormal shunt the minute circulation through the lungs and the periphery may be considered equal. The calculation of the pulmonary and peripheral blood flow separately is considered under the section on the use of catheterization in the diagnosis of congenital cardiac lesions.

Sufficient studies have now been reported to establish the normal range of the resting cardiac output.[34-38] The average is about 3.1 liters per square meter of body surface, but there is a wide range between 2.1 and 4.0 liters or even greater. It is difficult, of course, to obtain truly basal measurements because the conditions of the procedure militate against complete mental and physical relaxation. Anxiety and excitement increase the output, often markedly.[36] The various factors that are important in regulating the cardiac output have been studied at some length.[37, 38]

Numerous studies have now been reported on the resting cardiac output in patients with various types and degrees of heart disease.[39] In general these have confirmed earlier observations made with less exact methods. The observations show that the resting cardiac output is usually reduced in patients with congestive failure, but it may fall within the range of normal, and in certain cases it is even elevated. The latter situation is found in particular in some patients with cor pulmonale,[40] chronic anemia,[41, 42] hyperthyroidism,[38] arteriovenous aneurysm[43] and beriberi heart disease.[44]

The practicability of measuring the cardiac output during exercise by this method has greatly advanced knowledge of the mechanism of heart failure. The earliest symptoms of myocardial insufficiency usually develop during exertion, and hence it is logical that studies of the development of congestive failure should be made under conditions of stress. Hickam and Cargill[25] were the first to confirm by the method of cardiac catheterization what had already been reported by more indirect methods: that in normal human beings the cardiac output both per minute and per beat increases with increased oxygen utilization — for example, in exercise. They also showed that in patients with congestive failure or with mitral stenosis the blood flow failed to increase normally, if indeed it increased at all. These findings have been confirmed and extended by others.[28] Ellis and Harken[28] have, moreover, pointed out that in mitral stenosis, tachycardia, whether produced by exercise or excitement, may actually reduce the output per beat and even the total minute volume output. It has been frequently observed that the resting cardiac outputs of patients with heart failure or mitral stenosis fall within the normal range, but this represents the maximum that the patient's heart is capable of accomplishing, since the normal increase on exercise fails to take place.

Accurate studies of the hemodynamic effects of drugs acting on the heart and circulation are now possible, and are being undertaken. In particular a number of reports have appeared concerning the effects of the cardiac glycosides. McMichael and Sharpey-Schafer[45] showed that intravenous administration of digoxin increased the cardiac output and lowered the right-auricular-filling pressure in patients with congestive failure. They believed that the primary effect of the drug was to lower the peripheral venous pressure, with an increase in cardiac output secondary to this. Studies by Harvey et al.[46] with the same drug in patients with failure of the left ventricle have led them, on the contrary, to the conclusion that it acts primarily as a myocardial stimulant, and work from our laboratory is in agreement with this. Bloomfield

and his associates[47] previously showed that intravenous ouabain acts primarily on the heart by increasing cardiac output in heart failure independent of the other observed changes in peripheral venous pressure or heart rate. Stead, Warren and Brannon[48] have also demonstrated that lanatoside C increases cardiac output and lowers venous pressure in similar cases.

A recent development of interest and importance has been the catheterization of the coronary sinus. Most investigators who carry out many catheterizations have had the experience of inadvertently introducing the catheter into the coronary sinus. Recently, however, this procedure has been carried out deliberately, and the coronary blood flow has been measured both in animals and in man by a technic utilizing nitrous oxide.[49, 50]

A further advance in this direction has been made by Goodale et al.,[13] who, using this technic, have determined the utilization of oxygen, lactic acid, glucose, pyruvate and carbon dioxide in animals, and similar studies are now in progress[51] in normal persons and those with heart failure. This is beginning to open up a whole new field of study concerned with the cellular metabolism of the heart in health and disease.

The method of venous catheterization is also being employed to study physiologic changes in the liver and kidney. It has been shown[52] that the catheter could be passed through the superior vena cava, the right auricle and down the inferior vena cava into one of the renal veins. Thus, the clearance of various substances by the kidney, including those which measure renal blood flow, can be estimated. Important evidence concerning changes in renal blood flow and sodium retention in heart disease has been produced.[53, 54]

Important, too, has been the information obtained concerning hepatic blood flow and heart disease.[55-58] In this type of experiment the catheter is introduced into a hepatic vein, and blood samples from this location analyzed for oxygen, dyes and so forth.

Intracardiac Electrocardiography

It is technically a simple matter to convert the tip of the catheter into an exploring electrode and register endocardial electrocardiograms from various sites located under fluoroscopic guidance. Reports of such studies[8, 16, 17, 59-66] have provided information useful in an analysis of the physiologic conditions that control the propagation of the normal and of ectopic heart beats and of hypertrophy of the right ventricle.

Catheterization of the Left Side of the Heart

In the course of studies on patients with congenital heart disease in whom communications exist between auricles or ventricles, most investigators have had the experience of having the catheter pass into the left auricle or ventricle, the pulmonary veins or aorta. Valuable information has resulted but this has always been conditioned by the underlying abnormality in the circulation. Retrograde catheterization of the left ventricle through the aorta has been performed in animals by Hellems et al.[67] However, at autopsy the animals showed subendocardial hemorrhages in the left ventricle and the mitral and aortic valves, and the authors do not recommend the procedure in man. Zimmerman, Scott and Becker[68] have attempted the procedure in normal human beings, but have been unable to pass the catheter through the aortic ring. In 11 patients with free aortic regurgitation they were, however, able to accomplish this and obtained pressure measurements and electrocardiograms from the left ventricle. An additional patient developed ventricular fibrillation and died as an attempt was made to move the catheter into the ventricle. This may have been because the catheter entered and occluded a coronary orifice, but the possibility of myocardial irritability from stimulation of the endocardium of the left ventricle exists. It was mentioned above that ectopic ventricular beats occur with great frequency when the catheter is in the right ventricle. There is no reason to believe that the left ventricle is less irritable than the right, and bursts of ventricular tachycardia and other ectopic ventricular rhythms occur with great frequency during operation on the mitral valve when the surgeon passes his finger through the valve.[69]

Use in the Diagnosis of Congenital Heart Disease

This technic has been of invaluable aid in elucidating the physiology of the circulation in various types of congenital anomalies of the heart and great vessels, and in enabling accurate diagnosis to be made. The latter has ceased to be of academic and has become of great practical interest with advances in the surgery of congenital heart disease.

The same principles and methods of study that have already been described underlie the use of this procedure in the diagnosis of congenital heart disease. Numerous articles and monographs dealing with this have appeared.[11, 70-79]

When an abnormal communication between the left and right heart or the greater and lesser circulations exists, with a shunting of blood chiefly from left to right, the location of such a communication can be accurately defined by the fact that there will be a sudden increment of arterialized blood with high oxygen content added to the venous blood at and beyond the site of the shunt. This is accomplished by the taking of multiple samples of blood at various points from the pulmonary artery back through the right ventricle and auricle to the vena cava. Thus, patency of the ductus arteriosus or of the interventricular or interauricular septum

can be diagnosed. If no abnormal communication exists or the flow is from right to left, the oxygen contents of the various samples will be the same. The results of these findings can be used to calculate blood flow by the Fick principle, as described above. In patients with abnormal shunts between the lesser and greater circulations the flow through the lungs and the periphery is not equal. Hence the flow through these circulations can be calculated separately as well as the degree of shunted blood.

In certain types of conditions with left to right shunts, such as interatrial defects and patent ductus arteriosus, the pulmonary blood supply may be several times the blood flowing in the systemic circulation. Conversely, when there is a right to left shunt, with an obstruction in the pulmonary circulation, the pulmonary blood flow is much reduced as compared to that in the general circulation. Under these circumstances collateral channels through the bronchial veins are brought into play in a physiologic attempt to compensate for the inadequate pulmonary arterial blood supply. Hence the amount of blood flowing into the lungs through the pulmonary arteries is less than that passing through the pulmonary capillaries and veins by the quantity contributed by the bronchial venous anastomoses. Bing has worked out an ingenious method of calculating this difference.[72]

The possibility has already been discussed of introducing the tip of the catheter into the left auricle or ventricle or aorta in patients with abnormal communication between the right and left sides of the heart. Valuable information not only of theoretical but also of practical importance may thus be gained.

Further information of use in the diagnosis of congenital heart disease is obtainable from pressure readings. Such measurements are particularly helpful in patients with pulmonary stenosis. In this condition the systolic pressure in the pulmonary artery will be lower than that in the right ventricle. Under all other circumstances these pressures are equal.

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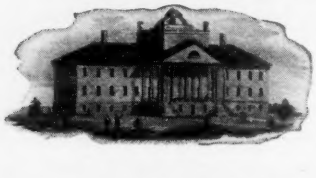
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

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CASE 36351

PRESENTATION OF CASE

A twenty-eight-year-old woman was admitted to the hospital because of shortness of breath.

The patient had been born following an uneventful pregnancy but was said to have weighed 12 pounds at birth. At the age of eight years she was seen in an eye clinic, where bilateral dislocation of the lenses was found. The lenses were removed. The heart sounds were of good quality and regular. An impulse was visible over the entire precordium, with a definite thrust on palpation. There was slight enlargement, but no murmurs were heard. She grew rapidly, but at the age of ten she was rejected for a basketball team because the doctor said that she had a murmur in the heart. She was, however, able to lead a normal, active life. At the age of twelve she was 6 feet tall. She was married at the age of seventeen, and nine, six and four years before admission she underwent uneventful deliveries. Shortly after the last pregnancy however, she developed some shortness of breath and palpitation on exertion. There was intermittent swelling of the ankles. She was never cyanotic. Two and a half years before the present admission she was seen in the Out Patient Department complaining of exertional dyspnea. Physical examination at that time revealed the pulse rate to be 90 and the blood pressure 130 systolic, 50 diastolic. The point of maximum cardiac impulse was in the sixth interspace, 13 cm. from the midsternal line, and there was a complete cyclic Grade II to III murmur heard best in the third intercostal space just to the left of the midsternal line. There was also a Grade III apical systolic murmur, which radiated over the precordium. The aortic area was clear. The pulmonic second sound was greater than the aortic. The fingers and toes were long, and there was peripheral edema. An electrocardiogram at that time revealed broad T waves but was considered to be within normal limits. She did not return to the Out Patient Department and led an apparently normal life until four months before admission, when the dyspnea became more marked and she was occasionally awakened at night by shortness of breath. She coughed and raised a small amount of sputum with these episodes. Two months before entry she visited her family doctor, who prescribed digitalis, and since then she took one tablet each day. It caused temporary improvement. For three weeks before admission her family doctor gave her an injection, which produced dryness of the mouth and a diuresis.

The patient's mother had "nervous trouble" and had abnormally long fingers. The father of the patient's mother also had abnormally long fingers. Two of the patient's children had long fingers, and the oldest child had a heart murmur.

Physical examination revealed the patient to be tall and orthopneic, with shallow rapid respiration. There was an occasional nonproductive cough. There were operative scars above both corneas, with V-shaped pupillary openings. Both lenses were absent. Only the lower front teeth were present, and those were in poor condition. The neck veins were distended and pulsating. The entire precordium was heaving. The heart appeared to be of enormous size, extending to the axilla on the left and 8 cm. to the right of the sternum. There was a Grade I thrill at the apex and a Grade III thrill at the base. The heart sounds were somewhat muffled by the murmurs. The pulmonic second sound was very loud, and the second tricuspid sound was snapping in quality. Both systolic and diastolic murmurs were present over the precordium and were loudest (Grade IV) in the second left interspace. One examiner believed that the murmur was principally diastolic in time. The rhythm was regular. There were moist rales at both bases posteriorly. The liver extended to halfway between the pubis and the umbilicus. The remainder of the physical examination was not remarkable except for very long limbs and especially long hands and fingers. The toes were not lengthened. There was no clubbing and no cyanosis. There was mild edema of both ankles.

The temperature was 101°F., the pulse 110, and the respirations 40.

The urine gave a ++ test for albumin, and the sediment contained 5 to 10 white cells per high-power field and rare granular casts. Examination of the blood disclosed a red-cell count of 4,980,000, with a hemoglobin of 9.2 gm., and a white-cell count of 11,000, with 58 per cent neutrophils. A blood culture was negative. An electrocardiogram showed partial auriculoventricular block and some definite intraventricular block. A chest film demonstrated a heart that was enlarged in all diameters with a cardiac-thoracic ratio of 22:27.3. There was a small

amount of fluid in both pleural sinuses. The aorta was inconspicuous but appeared to follow its normal course.

The patient continued to run a low-grade fever, the temperature varying from 100 to 101°F. Penicillin, 100,000 units, was begun on the third hospital day. A blood culture taken on the third hospital day grew out a coagulase-positive *Staphylococcus aureus* in one flask. The penicillin dosage was then increased to 300,000 and finally to 2,400,000 units per day. Salicylates were also given. The temperature returned to near normal after the patient had begun to receive salicylates, but it gradually rose again to 102°F. On the fourth hospital day a transient pleural friction rub was heard in the right base, and on the following day pleuritic pain was present in the lower left chest, and several flecks of blood were noted in the sputum. An x-ray film showed no change from the previous examination. On the sixth day there was diminished resonance in the left base in the midaxillary line and bilateral basal moist rales. The breath sounds were not diminished. Mercurial diuretics produced some loss in weight. The limbs were cold and clammy, and the patient appeared slightly confused. An electrocardiogram on the ninth hospital day showed auricular fibrillation. The serum sodium on the ninth hospital day was 133 milliequiv. per liter. The temperature returned to near normal on the eleventh and twelfth hospital days. The appearance of mild shock, confusion and asthenia persisted, and the patient died on the twelfth hospital day.

Differential Diagnosis

Dr. Howard B. Sprague*: I suppose I should recognize the honor of being asked to discuss what may be a unique case so far as the autopsy records of this hospital are concerned. No doubt you have all made the diagnosis, since this was a patient with dolichostenomelia; that, at least, was the term used by Marfan[1] in 1896, when he first described a patient with long slender fingers and toes, which he compared to those of the spider "*pattes d'araignée*," and in 1902 Achard[2] called this arachnodactyly. The first American case was reported in 1926.[3] I can remember the impression that I first received of a patient of this sort at the Children's Hospital, years ago — a tall, very slender child with long fingers and toes and the bilateral dislocation of the lenses, with the tremulous iris when the patient moved the head or eyes back and forth, and the cardiac murmur.

It seems to me that it is necessary to discuss this case in relation to the literature because of the 200 patients reported only 14, by 1947, had come to autopsy. However, the clinical description and the autopsy findings in the early cases were not well correlated.

This condition is presumably congenital and has an obscure etiology. Some have believed that it was due to an underlying defect of the mesodermal structures although this does not fit entirely with the pathology that is noted in the various organs. Certainly, these patients look like pure ectomorphic, long, thin, linear people with not much support on the mesodermal side. It was not until 1926[3] that the connection between arachnodactyly and the ocular pathology and congenital heart disease was noted. In addition to these defects there may be various deformities, particularly increased mobility of the joints. Often, there is a deformity of the chest, with scoliosis and deformities of the ears, a high arched palate, long narrow teeth and so forth. The difficulty with the eyes occurs in 40 to 50 per cent, abnormalities of the ears in 25 to 70 per cent, and heart murmur in 30 to 60 per cent of the cases. An excellent review of the literature was presented by Rados[4] in 1942.

In the case under discussion bilateral dislocation of the lens was noted at the age of eight years, some cardiac enlargement but no murmur at that time, a murmur developing by the age of ten years, and a height of six feet at the age of twelve. The patient, however, was able to go through three normal deliveries, and characteristically these patients have had quite good exercise tolerance up to the twenties or early thirties, and then a rapid downhill progress. By the age of twenty-four this patient had some cardiac failure, and at twenty-five, she had a very large heart with a murmur in systole and diastole in the third space at the left of the sternum, Grade III at the apex, and thrills that were Grade I at the apex and Grade III at the base. There was in addition an increased pulmonic second sound, partial intraventricular block in the electrocardiogram and, later, auricular fibrillation, with some intraventricular block of the left-branch type. There was also the story of the long fingers and the heart murmur in the patient's eldest child and in the patient's mother and grandfather. As a terminal affair there was fever, a positive blood culture and a story suggesting pulmonary embolism or thrombosis.

As this case illustrates, there are families in which the incomplete syndrome, or *formes frustes*, appears, with long fingers, and with or without cardiac abnormalities, which may run through two or three generations.

In 1943 Baer, Taussig and Oppenheimer[5] reported 2 cases in adults, who showed a medionecrosis of the aorta with aortic dilatation, and this aortic condition has begun to appear with rather impressive frequency in the literature. Etter and Glover,[6] in 1943, reported a death with dissecting aneurysm, Parker and Hare[7] in 1945 aneurysmal dilatation of the aorta by x-ray examination, and Uyeyama et al.,[8] in 1947, aortic dilatation, which was observed to increase in size during the period of the x-ray observation. In 1947 Tobin, Bay and Humphreys,[9] collecting the 12 autopsy cases from

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the literature and adding 2 of their own, found a patent foramen ovale or auricular septal defect in 5, a patent ductus in 1, lesions of the mitral or aortic valve in 8, a tricuspid lesion in 1, aortic cystic disease in 6, at times with dissecting aneurysm, and a normal heart in only 2.

Although rheumatic fever occurred in some of these children and there had been a suspicion of complicating rheumatic heart disease, the valve lesions at autopsy appeared to be more often of some bizarre congenital, myxomatous nature, at least in the recent cases that have been studied.

Now, I would like to have an opinion from the X-Ray Department.

Dr. James J. McCort: Gross enlargement of the heart is seen involving all four chambers. The aorta may be a little larger than normal, especially as seen in the left anterior oblique film. The pulmonary artery also seems to be slightly larger than normal. I believe the superior vena cava is also prominent. There is an accentuation of the vascular markings in the peripheral lung fields. In addition there are a few linear strands of increased density, which may represent scarring from either previous embolic or infectious processes. There is a small amount of fluid in both costophrenic sinuses.

Dr. Sprague: Thank you. In other words, there was enlargement of all chambers of the heart of a nonspecific type. The difficulty in making the cardiac diagnosis here is that the cardiac enlargement appeared to be rather nonspecific by x-ray examination, and the murmurs and thrills were also nondiagnostic. There is one point, however, that made me decide that I would make a diagnosis consistent with the cases of Baer, Taussig and Oppenheimer.[5] In their 2 cases, in spite of careful x-ray studies at Johns Hopkins Hospital, including barium in the esophagus, at autopsy there was tremendous dilatation of the ascending arch of the aorta, with aortic regurgitation, which was unsuspected by the examiners before death. The literature is disturbing because it allows one to make the diagnosis of aortic dilatation on insufficient evidence. Statistically, these patients have been considered to have predominant interauricular septal defects. The increased vascular markings of the lungs and the increased pulmonary second sounds would be consistent with that, but I would think that these murmurs developing in the last years of the illness were, in the absence of any terminal cyanosis, against that as a predominant lesion. There is not yet enough statistical evidence from autopsied cases for one to be at all sure of what will be found in the heart. But I am going to say that this was Marfan's syndrome; that the character of the murmurs and thrills, the rapid development, and the failure are consistent with the peculiar aortic pathology, which is similar to Erdheim's[10] cystic medionecrosis on a congenital basis; and that statistically there was probably some interauricular septal defect and also probably some congenital abnormality of the valves. It would appear that there was terminal infection in the blood stream and that there were also pulmonary infarctions. I will rest my case on that.

Dr. Tracy B. Mallory: Dr. Heath, can you tell us something about the ocular situation.

Dr. Parker Heath: These patients are seen rarely but do appear from time to time in the Out Patient Department. They show a variable degree of dislocation of the lens, usually upward and inward, but this also is variable. The dislocation is not always a surgical problem. The problem is rather whether the visual ability through or around the lens should be improved by glasses or surgery, or left alone. The lens in these patients is often smaller than normal and globular or discoid. The pupils often do not dilate well because there is a defect in the dilator muscle fibers. These patients usually exhibit other deformities — high palate, high brow lending a judicial air, long spider fingers and so on. Generally, they apparently possess an irregular dominance. About half show heart abnormalities, probably because the heart and the eyes develop about the same time during the organogenic period and are likely to be affected by the same sort of circumstances. Their visual fields and vision may be quite good, optic mobility is not disturbed and sight with corrective lenses is often fairly good, and may be nearly normal. It would be interesting to have a microscopical study of the eyes in this case.

Clinical Diagnoses

Marfan's syndrome.
Congestive heart failure.
Auricular septal defect.
Rheumatic heart disease, with aortic regurgitation.
Active rheumatic fever.
?Bacterial endocarditis.
?Dissecting aneurysm of aorta, with medionecrosis.

Dr. Sprague's Diagnoses

Marfan's syndrome.
Cystic necrosis of aorta, with dilatation and aortic regurgitation.
Possible interauricular septal defect.
Probable congenital valvular deformity (myxomatous).
Blood-stream infection.
Pulmonary infarcts.

Anatomical Diagnoses

Marfan's syndrome.
Aneurysm of ascending aorta, with rupture, old.
Idiopathic medionecrosis of aorta.
Cardiac hypertrophy and dilatation, marked.
Arachnodactyly.

Thrombi, left auricle.
Pulmonary embolism and infarction.
Splenic infarction.
Operations: iridectomy, bilateral, old, removal of lens, old.

Pathological Discussion

Dr. Mallory: As Dr. Sprague predicted, this was the first case of so-called Marfan's syndrome that has come to autopsy in this hospital. The most striking feature of the autopsy was the enormous enlargement of the heart, which weighed 850 gm., and the localized dilatation of the aorta that began approximately 3 cm. above the aortic ring, extended up to the arch and then very suddenly contracted down to normal diameter. The picture (Fig. 1) shows the aortic valve and the dilated segment. The semilunar cusps are quite clearly seen, and at

Figure 1.

the tip of the arrow is what seems to be a second valve and over on the right hand side a similar one. There is a linear rent in the intima about 3 cm. above the semilunar valves just to the right of the arrow. This was interpreted as a healed dissecting aneurysm. The aortic wall was split for a very short distance, and the inner segment of the aorta made this false valve. Microscopical sections through this area showed the characteristic appearances of medionecrosis cystica, as was reported in the case at Johns Hopkins Hospital[5] and also from Chicago by Tobin, Bay and Humphreys.[9] The first photomicrograph is of the wall of the aneurysm showing at about the midportion a longitudinal cyst-like formation, consisting very largely of loose collagenous fibrous tissue with a diminished number of muscle and elastic fibers. The second shows the outer layer of the wall behind the false valve, which consists almost entirely of collagenous fibrous tissue; very close to the adventitia there are a few elastic fibers and smooth-muscle cells. The elastic tissue, which stains black, should appear in these sections as a continuous layer across the entire media of the aorta but is present only in focal areas and has evidently been extensively destroyed. In the original section one could see in the cyst-like space a very faintly staining bluish mucinous secretion such as is seen in Erdheim's[10] medionecrosis cystica. Authorities have disagreed about whether any histologic differences have been discernible between this type of medionecrosis cystica and the usual one that Erdheim described, which is commonly seen in middle-aged people with a history of fairly severe hypertension for many years. I am quite sure that I cannot see any difference in the focal lesion. The fact that this is likely to be a local form not diffuse throughout the entire aorta is a much more striking difference than is seen in a given section.

There was no evidence of a bacterial endocarditis. Post-mortem blood culture showed pyocyaneus rather than staphylococcus. There was no interauricular septal defect. The hypertrophy and dilatation of the chambers of the heart were quite uniform. All chambers were involved to about an equal degree. There was marked hypertrophy of the right side as well as of the left. There were two rather large pulmonary infarcts, evidently terminal, and a very small infarct was found in the spleen. The right coronary orifice was high, about 2 cm. above the commissure; the left was in normal position.

Dr. Sprague: There were no myxomatous changes of the valves?

Dr. Mallory: In one of the valves there was a slight myxomatous thickening but not very different from those commonly seen in older people. One does not often see it in a woman of this age.

Dr. Arthur S. Pier: Why did the heart fail if there was no septal defect?

Dr. Mallory: Whether there was enough relative aortic regurgitation to account for it I cannot say. I hardly think so, although the valves were large except the pulmonary, which was of normal diameter. I do not think the mechanism of failure is at all clear. The myocardium was microscopically quite normal in appearance. There was no evidence of rheumatic involvement or any scarring.

Dr. Sprague: The fact that these patients sometimes drop dead suggests that there is a coronary element to the dilatation.

Dr. Mallory: In some cases the dissection of the aorta has worked retrogradely back around the mouths of the coronary arteries and produced coronary occlusion from external pressure, but that was not present here.

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CASE 36352

Presentation of Case

A fifty-five-year-old man was admitted to the hospital with a chief complaint of fever of several weeks' duration.

Six months before entry the patient noted the insidious onset of moderate exertional dyspnea and cardiac palpitation. Three months later he experienced the gradual onset of dull, right-sided, substernal and costochondral pain unrelated to exertion but made worse by deep inspiration. His physician prescribed codeine, which provided slight relief. Five weeks before admission the patient first complained of aches and pain in the shoulders, elbows, knees, hands, wrists and temporomandibular joint. These symptoms caused him to remain at home and finally to take to his bed two weeks later. Fifteen days prior to hospital admission a physician found him to be febrile, and gave him 300,000 units of penicillin and a "liquid sulfa compound," which he took in a dosage of 2 teaspoonfuls every three hours for a period of four days. The patient noted the onset of sore throat at approximately the same time. He continued to feel wretched, and the fever persisted, with daily fluctuations in temperature up to 101°F. Ten days before admission the metatarsophalangeal joints became painful, swollen and erythematous. Studies in another hospital showed a "normal electrocardiogram" and pneumonitis at the right base on x-ray examination. A short episode of auricular fibrillation occurred, but normal rhythm was rapidly reestablished with quinidine. Six lower teeth were extracted, and he was given daily injections of penicillin and a total of thirty-six aureomycin pills over a period of seven days. Eight days prior to admission he complained of "stitch-like" pain and tenderness in the right upper quadrant of the abdomen, aggravated by motion of the trunk but nonradiating, noncolicky and unassociated with nausea or vomiting. Four days before hospitalization the sole of the right foot became numb. Antibiotic therapy was discontinued after seven days because the patient had shown no improvement. Immediately following an injection of iron and liver in the left buttock on the day before admission he experienced a sharp pain in the left groin radiating to the left testis, where it persisted. On the same day a crop of petechial hemorrhages appeared on the right lower leg. On the morning of admission he developed a cough productive of several teaspoonfuls of sputum containing bright-red blood. The patient had lost 25 to 30 pounds in weight over the previous nine weeks. Although his fever had been continuous it was fluctuating and unassociated with chills or night sweats. Throughout the present illness there had been considerable constipation requiring frequent enemas. There had been no icterus or melena. During the previous few days a status of urinary frequency had given way to oliguria with passage of dark urine.

The family history was noncontributory. There was a past history of a penile chancre at the age of twenty-four treated with arm and "hip" injections. Serologic follow-up study showed a persistently positive blood Wassermann test throughout the years, but examination of the spinal fluid had been negative on two occasions. There was no history of asthma or exposure to chemicals. Throughout the illness he took from 4 to 6 aspirin tablets per day, with slight relief of symptoms.

Physical examination revealed a pale, chronically ill man complaining of pain in the joints and abdomen. There were petechial lesions on the medial aspect of the right lower leg. Both eyes showed conjunctival injection, and moderate episcleritis was found in the right eye. The fundi were normal. A 5-mm. indurated, yellow, tender spot on the hard palate was surrounded by erythema. Fine and crackling rales were heard over both lung bases posteriorly. The heart was not enlarged. There were frequent premature beats, and a Grade I systolic murmur was heard at the apex. Involuntary spasm and tenderness were evident in the right upper quadrant of the abdomen, and percussion dullness extended 8 fingerbreadths below the right costal margin. No organs or masses were palpable. Peristalsis was hyperactive but of normal pitch. A pigmented scar was noted on the penis, and the left testis was acutely tender and indurated. The prostate showed a + enlargement. The deep tendon reflexes were diminished in intensity, and all the joints were tender. Redness and swelling were apparent over all the metacarpophalangeal joints and the first left metatarsophalangeal joint. No cyanosis, digital clubbing or edema was seen.

The temperature was 101.6°F., the pulse 95, and the respirations 24. The blood pressure was 100 systolic, 60 diastolic.

The urine varied from light brown to grossly bloody with a specific gravity of 1.010. There was a + to ++++ test for albumin, and a green sugar reaction was obtained on one occasion. There were numerous white cells and red cells with many

coarsely granular, finely granular, leukocytic, erythrocytic and waxy casts in the sediment. The hemoglobin fell from 10 to 7 gm. over three days. The red-cell count was 2,300,000. The white-cell count varied from 16,000 to 23,000, with an average of 85 per cent neutrophils, 7 per cent lymphocytes, 4 per cent monocytes and 4 per cent eosinophils. The stools were guaiac negative. The nonprotein nitrogen varied from 53 to 100 mg. per 100 cc.; the uric acid was 5.4 mg., the total protein 4.93 gm., the albumin 2.89 gm., the globulin 2.04 gm., the cholesterol 177 mg., the calcium 7.8 mg., the phosphorus 4.9 mg., the alkaline phosphatase 9.5 units, and the amylase 22 units per 100 cc., and the van den Bergh reaction was 0.2 mg. per 100 cc. direct, 0.5 mg. per 100 cc. total; the cephalin flocculation was ++ at 24 and 48 hours, and the prothrombin time was 32 to 40 per cent of normal. The agglutination tests for typhoid, paratyphoid, brucella and tularemia were negative. A urine culture yielded no significant pathogens. An electrocardiogram was normal. X-ray films of the chest revealed changes suggesting fluid in the left thorax, reduction in size of the left lower lobe and a patch of consolidation in the right middle lobe. Aside from considerable hepatomegaly, a plain film of the abdomen was normal.

Treatment in the hospital consisted of aspirin, Demerol, chloral hydrate, Benadryl, penicillin and streptomycin. The patient continued to complain of severe pain in the right upper quadrant of the abdomen. A small hemoptysis occurred on the second day. On the third hospital day, he became delirious, followed by stupor. Death occurred on the fourth hospital day.

Differential Diagnosis

Dr. John B. Stanbury*: May we see the x-ray films first, Dr. Wyman?

Dr. Stanley M. Wyman: The first film shows definite pleural effusion on the left posteriorly. The right-major fissure is displaced posteriorly, the right lower lobe being considerably decreased in size. The density in the right lung is in the lower lobe, I believe, rather than in the middle lobe as recorded. The major bronchi cannot be visualized because the patient is incompletely rotated. The film of the abdomen shows a very large liver extending downward beyond the iliac crest, but the spleen is not enlarged. The left kidney can be traced and appears normal in size and shape. The last films of the chest, taken two days later when the patient was considerably sicker, show essentially the same findings, but there has been some accentuation of the process in the right lower lobe.

Dr. Stanbury: Is there nothing at all in the right upper lobe?

Dr. Wyman: I would discount it.

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Dr. Stanbury: This patient's disease was a widespread process involving many organ systems. In the course of the discussion we shall have to account for involvement of the heart, the lungs, the liver, the kidneys, the joints and perhaps the nervous system. I think it would not be worth while to take each of these systems and review the differential diagnosis of the signs and symptoms presented by each. Rather, I should like to consider this problem as one in the differential diagnosis of fever of unknown origin, to narrow down to a very few possibilities, and then to test the closeness of fit of these to the case as we have it here.

I might then consider the general causes of fevers. There are those caused by infections, those caused by neoplasms, those caused by drugs and those caused by the collagen diseases. I can forget drugs; there is no reason to believe that the patient was taking any drug in such a fashion as to account for the fever. Neoplasms I need consider only briefly. They do cause continued fever, particularly if of the lymphoma group or if of the liver or metastatic to it. There was very little to suggest neoplastic disease. The large liver was probably the most suggestive finding. It could have been full of metastatic cancer. Furthermore, there was the statement of the patient's having been constipated throughout the present illness. However, the guaiac test on the stool was negative, and I have no other good reason at the moment to make a diagnosis of gastrointestinal-tract disease or metastases to the liver.

This brings me to infections. In the first place the problem is to decide whether the arthritis was part of a single disease or whether it was an incidental and concomitant finding. It plays such a prominent role in the case history that I cannot see how I can discard it. I think I have to consider the arthritis as part and parcel of this patient's systemic disease. That helps me a great deal in talking about infections because relatively few infectious diseases give rise to an arthritis that has the pattern and distribution of rheumatoid arthritis such as was exhibited here. The first infection I might consider is undulant fever. Undulant fever does give rise to liver involvement and to a long-continued fever. However, the arthritis of undulant fever is not commonly in the metatarsophalangeal joints. More commonly it involves the spine. Rarely has it given rise to a rheumatoid pattern.

A second infection to be considered is that caused by the salmonella group of organisms. These also may cause long-continued fever and arthritis, but again the spine is more commonly involved. When involvement is elsewhere, it is commonly of a single joint.

The meningococcus also may cause chronic fever and arthritis. It gives rise to three different types of joint involvement; the first is just arthralgia, the second is a frank hemarthrosis, which is part of the focal hemorrhagic phenomena in that disease,

and the third is a purulent arthritis, which this patient did not have. Again, the distribution of joint involvement was wrong. Also, the patient failed to respond to penicillin, contrary to the usual occurrence in chronic meningococcal septicemia.

Miliary tuberculosis must be considered. I have no reason to think from the history that this was tuberculosis. I note nothing that looks like a primary focus. Tuberculosis does give rise to miliary tubercles in the liver. This might also furnish an explanation for the peripheral-joint manifestations, but usually it would be confined to a single or a few joints. *Streptobacillus moniliformis* infection is also a possibility. There was no portal of entry. The patients who develop this infection have a bluish-red rash over the trunk and extremities, but not the petechial rash described here. Furthermore, I think organisms would have been found since they are fairly easy to culture from the blood. A generalized arthralgia occurs, and at times a localized exudative arthritis in one of the large joints. The disease responds readily to the usual dose of penicillin.

There is one common infection that deserves more careful consideration. Subacute bacterial endocarditis can explain most of the signs and symptoms that this patient exhibited. The fever, the anemia, the oral lesion, the embolic phenomena, the chest findings, the large liver, the renal findings, the findings in the testis and so on are all readily explained by bacterial endocarditis. But I must consider the joints. While joint pain is common in bacterial endocarditis, frank polyarthritis is very rare. There is one loophole, however; at least 2 of the patients with severe rheumatoid arthritis who have been autopsied here have had subacute bacterial endocarditis, and I suppose that it is conceivable that this patient had bacterial endocarditis and rheumatoid arthritis. There are, however, findings that seem to me to rule out this disease. In the first place this patient had no clubbing of the fingers, but, what is more important, he had a normal-sized spleen. He had a Grade I apical systolic murmur, which is explained perfectly well by the fever and the anemia. A diagnosis of bacterial endocarditis without a significant murmur is extremely hard to make. It does occur. I have seen a patient who had the vegetations of bacterial endocarditis on the underside of an aortic cusp, and no murmurs were heard, but it is an uncommon occurrence. A diagnosis of bacterial endocarditis could be stretched to cover this entire picture, but I think it would take considerable stretching.

I should prefer to believe that this patient had a disease that falls into the group known as the collagen diseases: periarteritis nodosa. This is a diagnosis that one hesitates to make because it has such widespread manifestations that it can be made to cover practially any disease or syndrome one wishes to consider. This patient, however, presented such widespread disease that an inclusive diagnosis is demanded to cover all its many features. I might review this patient's course and see how well the diagnosis of periarteritis fits. The first symptoms were fatigue and cardiac irritability. Involvement of the myocardium is not uncommon in periarteritis, and this patient did have a transient attack of auricular fibrillation. A little later he developed arthritis. Joint involvement is fairly common in periarteritis. Diffuse involvement, including the joints of the extremities is consistent with this diagnosis. A little later he developed fever, and fever is also prominent in periarteritis. Nineteen days before he died he received sulfonamide medication for four or five days. Lesions similar to those of periarteritis have been produced with sulfonamides and are said to accentuate the manifestations of this disease. It is quite possible that the sulfonamide accelerated the pathologic process here. Eight days before admission and twelve days before the patient died, a very significant event took place — namely, the development of stitch-like, right-upper-quadrant pain. Later, it was found that he had an enormous liver. Right-upper-quadrant pain is the most common single symptom of periarteritis. Also, the liver is the single most common site of pathologic involvement. Although infarction of the liver is rare, when it does occur it is most commonly due to periarteritis. In looking up a number of cases of periarteritis, I found few notes about large livers, but it was mentioned a few times. Therefore, I do not see why this liver could not have been due to periarteritis, but it is the single most troubling problem in this case. One way to explain it is to suggest the presence of thrombosis of the hepatic veins. Venous thromboses are common in some inflammatory processes, and are not uncommon in periarteritis nodosa.

The next event that occurred was numbness of the sole of the right foot. Peripheral neuritis is common in periarteritis. It seems to be due to thromboses of the nutrient arteries of the nerves. The sudden onset of testicular pain may be explained by occlusion of the spermatic artery. Another vascular phenomenon was the petechiae. They are not commonly seen in periarteritis, but do occur and may be indistinguishable from the petechial showers of other diseases. Ecchymoses may also be seen.

There was much evidence of renal involvement, which is characteristic of this disease. It was of sufficient degree to impair renal function to the extent that the nonprotein nitrogen was elevated. It is more difficult to account for the remarkably low serum sodium and protein concentrations. Perhaps these findings, pointing to hemodilution as was also suggested by the anemia, may be accounted for in part by enthusiastic rehydration therapy with glucose and water, rather than by a kidney disturbance per se, although a damaged kidney may have been less able to compensate for a heavy added fluid load.

Finally to be mentioned is the episcleritis, which is seen in rheumatoid arthritis as well as in periarteritis, and the pulmonary shadows and the hemoptyses. The last can be interpreted as having been due to pulmonary infarcts, or perhaps better, as thrombi of the bronchial arteries.

There are a number of things that trouble me. I am particularly troubled by the large liver. I am also troubled by the elevated serum phosphatase, and I do not know how to account for it. Nevertheless, the only diagnosis that I can make with confidence is periarteritis nodosa. I think that there was generalized arterial disease, and that there may have been infarctions of the liver as well.

Dr. Tracy B. Mallory: Are there any questions or suggestions?

Dr. Arthur S. Pier: How about the joints?

Dr. Stanbury: I asked Dr. Marian Ropes that question the other day, and she told me that joint involvement may be similar to that of rheumatoid arthritis in this disease. My personal experience is too limited.

A Physician: Would lupus erythematosus explain it?

Dr. Stanbury: I think it would if this were a young woman. I think that lupus in an elderly man is very unlikely. There was no skin lesion to suggest it.

Dr. Alfred E. Kranes: Does the absence of hypertension trouble you at all?

Dr. Stanbury: Yes; it does. The patient should have had hypertension and may have had it before he became so ill. But all patients who have had periarteritis have not had hypertension.

Dr. Kranes: Have you seen cases with renal involvement as striking as this in the absence of hypertension?

Dr. Stanbury: Renal impairment to this degree is described.

Dr. J. H. Means: I do not think that this man had syphilis, but it is interesting that one never thinks of that any more in the differential diagnosis of a febrile infectious process. Syphilis should be mentioned.

I have one other comment to make. I came to grief at a clinicopathological conference in St. Louis some years ago discussing a case in which there was a liver of this size and fever of this general sort that turned out to be tuberculosis, a small lesion of which eroded a bronchus and gave rise to miliary tuberculosis. I suppose that might have happened here without much evidence of antecedent tuberculosis of the lung. Generalized tuberculosis resulting from a primary infection of the abdomen has quite often involved the liver. Such patients usually have large spleens and are likely to have leukopenia. I was looking for that in this case, but it does not seem to fit very well.

Clinical Diagnosis

?Periarteritis nodosa.
?Subacute bacterial endocarditis.
?Septicemia.

Dr. Stanbury's Diagnosis

Periarteritis nodosa.
?Infarction of liver.

Anatomical Diagnoses

Polyarteritis nodosa, diffuse.
Glomerulonephritis, hemorrhagic, acute, diffuse.
Polyserositis, acute.
Infarction of testes, bilateral.
Hepar lobatum, syphilitic.

Pathological Discussion

Dr. Mallory: The autopsy showed a polyarteritis, with fibrinous pericarditis, pleuritis and peritonitis.

The heart was somewhat enlarged and showed no gross valvular lesions but some microscopical evidence of endocarditis. The coronary arteries appeared normal except for petechial hemorrhages along some of the smaller branches. The lungs were markedly edematous and very heavy. The left was collapsed and had a few petechial hemorrhages. The spleen weighed 380 gm., which is about the border of palpability; a spleen of that size sometimes is felt but frequently is not. The intestinal tract showed scattered petechial hemorrhages in the mucosa, and the mesenteric lymph nodes were generally enlarged. The kidneys were greatly enlarged, weighing 600 gm. and were dotted over with petechial hemorrhages. They looked like kidneys of acute glomerulonephritis. Both testes showed areas of hemorrhagic necrosis, and the joint synovial membranes showed inflammation and focal hemorrhages.

Microscopically, we found widespread lesions of small arteries and veins in many organs of the body, characteristic in type of polyarteritis nodosa. As is often found, these lesions were quite variable; in some places they were acute, and in others old enough to have developed thrombosis and considerable organization. The kidneys presented a complicating factor. There was a very extensive, diffuse, and I think fairly long-standing glomerulonephritis, looking as though it were months rather than a few weeks old. There were typical vascular lesions as well, and there was a great deal of interstitial inflammatory infiltration. I think we have to assume that in the kidney there was more than the arterial lesion — that a true glomerulonephritis was present. There was nothing very striking in the microscopical pattern of the liver to explain its size. It was congested. We did not run across any vascular lesions although it is very probable that we missed some. We end up with two primary diagnoses, acute glomerulonephritis and polyarteritis nodosa.

DR. KRANES: How much did the liver weigh?

DR. MALLORY: It weighed 2500 gm.

DR. MEANS: Why has the name of the disease been changed?

DR. MALLORY: The name of the disease has been changed a couple of times and ought to be changed again. It was originally described as periarteritis nodosa because the first observers were impressed with the nodular thickening around the arteries. Then as more cases were studied, it became evident that it was not merely a periarteritis but that all layers of the vessels were involved — intima, media and adventitia. In fact, unless the media is involved, I hesitate to make the diagnosis. Panarteritis, general arteritis, polyarteritis and other names have been suggested. Then in a certain number of cases there has been very extensive involvement of veins as well so that the word arteritis should probably be omitted and we ought to change it to angiitis.

DR. KRANES: What about the peripheral vessels? Were they too involved?

DR. MALLORY: We did not run across any clear-cut lesion of the peripheral vessels, probably because of insufficient sampling. An anatomic landmark was a typical hepar lobatum of acquired syphilis but there was nothing to indicate any active syphilis at the time of death.

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CIVIC RESPONSIBILITY

A privilege that is denied to millions of the world's inhabitants is considered as of little value, apparently, by many Americans who possess it. Perhaps it is true that familiarity breeds contempt and that free gifts are often held cheaply.

But the right of Americans to choose their form of government and the persons to administer it did not come at all cheaply. It is the product of centuries of aspiring, and the reward of countless struggles. It made its appearance as a limited gift in the market places of the Greek cities and in the Roman Forum; it was at the root of the Icelandic Parliament a thousand years ago. It was wrung from King John by his barons at Runnymede; it has been affirmed by revolution after revolution against oppression, and defended on far-off battlefields in modern times.

How highly is this obligation that free men have placed upon themselves regarded in America? Some figures that have had wide publicity were obtained from the board of election of Summit County, Ohio, an industrial area including the city of Akron. They have reference to the national election of 1948.

In that election, in Summit County, 18 per cent of the physicians did not vote and 13 per cent *were not registered*. Twenty-two per cent of their wives did not vote and 16 per cent were not registered. Of members of chambers of commerce the comparable figures are 21 and 15; of bank employees, including executives, 32 and 26; of retail grocers 34 and 20. Into the hands of persons not of their choosing these citizens thus put the means of their own possible undoing.

This country has drifted into a crisis the outcome of which no man can see. Each one who is qualified to vote, however, can make his or her contribution to the ultimately successful outcome of the actions in which the nation is engaged, or by indifference can continue the jeopardy on which its future lies.

The need is for every citizen to do his duty at the polls on every occasion, not simply to vote a party line or for or against compulsory so-called health insurance or to approve the present stand, however tardy, against the effronteries of communism, but to elect qualified candidates for office who will strive to maintain a government of and for and by the people.

"THE AFFAIR CRIES HASTE"

Major General Raymond W. Bliss, surgeon general of the Army, has recently announced that over 75 per cent of the medical graduates who interned in Army hospitals under the Military Intern Training Programs have remained in the Army longer than the legal requirement for active duty.

The actual numbers, however, are not overwhelming. Since the program started, a little over three years ago, three groups, totaling 311 persons, have completed internship training as officers commissioned in the Medical Corps Reserve. Of this number 235 elected to remain on active duty either as regular or as reserve officers, and several of the remainder have requested return to active

duty. Only 7 of the total failed to retain their reserve commissions.

Meanwhile, twin bills have been filed in the House of Representatives by Saylor and Cavalcante of Pennsylvania to amend the Selective Service Act so that certain physicians and dentists may be called into service. Induction would be in the following order: first, those who saw no active duty following participation in ASTP or V–12 programs or who, regardless of such participation, were deferred from military service in order that they might continue professional education; secondly, former ASTP and V–12 students who had less than twenty-one months of active duty; thirdly, those who have had less than ninety days' prior military duty; and, fourthly, those whose total military duty was less than twenty-one months.

Incidentally a Senate subcommittee of two, composed of Senators Hunt and Saltonstall, is considering legislation authorizing the commissioning of women in the medical corps of the Army, Navy and Air Force. Already 31 women medical officers are in naval service.

By whatever means, but preferably by the most just and logical, the safety of the nation must be assured. As Bradford recently quoted,

". . . . The affair cries haste,
And speed must answer it! . . ."

BRETTON WOODS AGAIN

THE *Journal* takes this occasion to salute the New Hampshire and Vermont State Medical societies, for the first time about to come into conjunction (accompanied by their auxiliaries and the New Hampshire Surgical Club) as has been the custom of celestial bodies since time began.

The dates of the initial combined convention are September 9, 10, 11 and 12, and the place at which this astronomical phenomenon can be observed will be Mt. Washington Hotel in Bretton Woods, New Hampshire. Each society will have its usual meetings for the transaction of business, joining together for the general scientific sessions, the convention banquet at which General Paul R. Hawley will be the speaker of the evening, and the indispensable golf tournament, which this year will be under the sponsorship of the New Hampshire Surgical Club.

New Hampshire and Vermont, to many who still appreciate the original meaning of the term "Yankee," have retained the flavor of New England as have baked beans (Boston), maple syrup and Medford rum. In this very individualism the inhabitants of these states are completely representative of the section of the country in which they continue to reside, mindful of the fact that most of the remainder of the nation was settled by their great uncles and aunts.

New Hampshire and Vermont will meet together in perfect understanding with no odds asked or given!

A hog, in the shape of a man, recently undertook, upon a wager, to eat 10 lbs. of beefsteak, on which was 2 lb. of butter; an emetic saved his life.
Boston M. & S. J., *August 28, 1850*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

NEW CANCER MANUAL

The book *Cancer, a Manual for Practitioners* has been distributed free to all practicing physicians in Massachusetts who are on the Department's mailing list. There is a possibility that some physicians have not received a copy. The book will be sent them upon receipt of a written request to the Division of Cancer and Other Chronic Diseases, 100 Nashua Street, Boston 14. At the present time copies are not being furnished free to hospital residents, interns and physicians not in practice, since the number of books is limited.

NOTICES

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held in the conference room of the hospital on Thursday, September 7, at 7:15 p.m. The subject of the conference will be "Setting up a Premature Center: A report on the Institute for the Care of Premature Babies at the New York Hospital-Cornell Medical Center." Dr. Clara Waldinger and Miss Virginia Gillis, R. N., will be the speakers. Dr. Ann O'Donnell will be chairman.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.
SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.
SEPTEMBER 6–30. The Springfield Hospital. Page 324, issue of August 24.
SEPTEMBER 6–MAY 2. Hampshire District Medical Society. Page 170, issue of July 27.
SEPTEMBER 7. New England Hospital for Women and Children. Notice above.
SEPTEMBER 7–9. All-Austrian Congress of Physicians. Page 994, issue of June 22.

(*Notices concluded on page xi*)

NOTICES *(Concluded from page 356)*

SEPTEMBER 14. Progress in the Management of Hand Injuries. Dr. Henry E. Marble. Pentucket Association of Physicians. 8:30 p.m., Haverhill.
SEPTEMBER 18–27. International Congress of Psychiatry. Page 240, issue of August 10.
SEPTEMBER 26–29. American Roentgen Ray Society. Page 240, issue of August 10.
SEPTEMBER 27. American Medical Writers' Association. Page xi, issue of July 13.
NOVEMBER 6–8. New England Postgraduate Assembly. Hotel Statler, Boston.

DISTRICT MEDICAL SOCIETY

HAMPSHIRE

SEPTEMBER 6. 4:30 p.m. Belchertown State School.
NOVEMBER 1. 4:30 p.m. Northampton State Hospital.
JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 7

THURSDAY, SEPTEMBER 7
*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.
7:15 p.m. Monthly Clinical Conference and Staff Meeting. Conference Room, New England Hospital for Women and Children.

FRIDAY, SEPTEMBER 8
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Tumor Clinic. Out-Patient Department. Mount Auburn Hospital, Cambridge.

MONDAY, SEPTEMBER 11
*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, SEPTEMBER 12
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, SEPTEMBER 13
*12:00 m.–1:00 p.m. Grand Rounds. Amphitheater, Children's Hospital.

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Index to Advertisers

	PAGE
Abbott Laboratories	vii
Adams House	x
American Policyholders' Insurance Co.	xi
Ames Company, Inc.	iv
A–Z Research Laboratory	viii
Baldpate, Inc.	x
Boston Medical Supply Company	viii
Channing Sanitarium	v
Crane Discount Corporation	v
Cutter Laboratories	ix
David Memorial Nursing Home	x
Glenside, Inc.	x
Harvard Medical School	xi
Institute for Speech Correction, Inc.	x
Kenmore Pharmacy, Inc.	x
Leary Laboratory	viii
Eli Lilly and Company	Front Cover
Mead Johnson and Company	Back Cover
Medical Protective Company	v
Norfolk County Trust Company	v
Parke, Davis and Company	ii, iii
Perkins School	x
Ring Sanatorium	x
Washingtonian Hospital	x
Westwood Lodge, Inc.	x
Winthrop–Stearns, Inc.	vi
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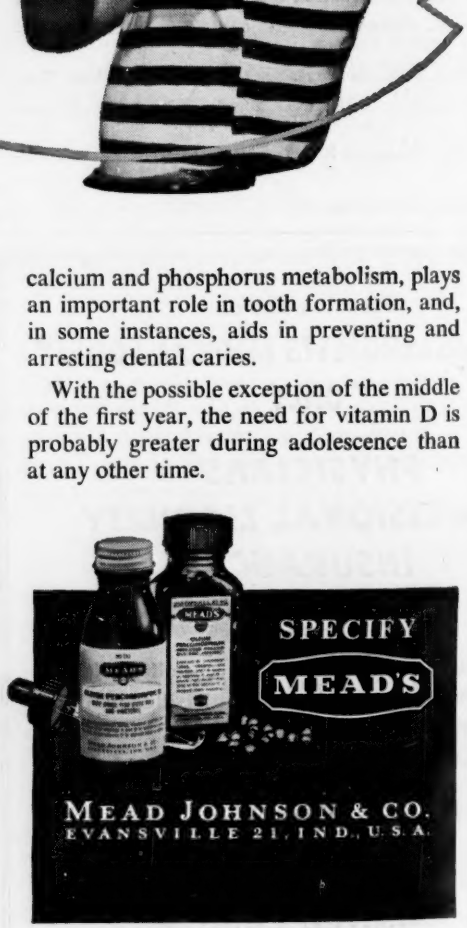
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